AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Chronic Pain Guideline

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CONTRIBUTORS

Editor-in-Chief:
Kurt T. Hegmann, MD, MPH, FACOEM, FACP

Evidence-based Practice Chronic Pain Panel Chair:
Steven D. Feinberg, MD, MS, MPH

Evidence-based Practice Chronic Pain Panel Members:
Gerald M. Aronoff, MD, DABPM, DABPN, FAADEP
James Ausfahl, MD
Daniel Bruns, PsyD, FAPA
Beth D. Darnall, PhD
Rachel Feinberg, PT, DPT
Jill S. Galper, PT, MEd
Lee Glass, MD
Robert L. Goldberg, MD, FACOEM
Scott Haldeman, DC, MD, PhD
James E. Lessenger, MD, FACOEM
Steven Mandel, MD
Tom G. Mayer, MD
Russell L. Travis, MD, FACS, FAADEP
Pamela A. Warren, PhD
Thomas H. Winters, MD, FACOEM

Panel members represent expertise in occupational medicine, physical medicine and rehabilitation, electrodiagnostic medicine, pain medicine, clinical psychology, psychiatry, neurology, electroencephalography, neurophysiology, neurosurgery, orthopedic surgery, physical therapy, exercise physiology, family medicine, legal medicine, medical toxicology, infectious disease, and chiropractic medicine. As required for quality guidelines (Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines and Appraisal of Guidelines for Research and Evaluation (AGREE)), a detailed application process captured conflicts of interest. The above panel has none to declare relevant to this guideline.

Methodology Committee Consultant:
Jeffrey S. Harris, MD, MPH, MBA, FACOEM

Research Conducted By:
Kurt T. Hegmann, MD, MPH, FACOEM, FACP
Matthew S. Thiese, PhD, MSPH
Ulrike Ott, PhD, MSPH
Kristine Hegmann, MSPH, CIC
Emilee Eden, BS
Pranjal Abhinav Muthe
Harkomal Kaur
Michael Northrup
Jenna K. Lindsey
Natalie Victoria Pratt
Skyler David Walker
Lisa Soffe, BS
Matthew Houston
Alzina Koric, MPP
Jeremiah L. Dortch, BS
Jesse Reifsnyder
Dillon Joseph Fix
Jeremiah Lafayette Dortch, MS

Specialty Society and Society Representative Listing

ACOEM acknowledges the following organizations and their representatives who served as reviewers of the Chronic Pain Guideline. Their contributions are greatly appreciated. By listing the following individuals or organizations, it does not infer that these individuals or organizations support or endorse the chronic pain guidelines developed by ACOEM. Additional organizations wish to remain anonymous.

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INTRODUCTION

The Chronic Pain Guideline is designed to provide health care providers (the primary target users of this guideline) with evidence-based guidance on the evaluation and treatment of working-age adults who have chronic pain. While the primary patient population target is working adults, the principles may apply more broadly. This guideline does not address guidance for numerous specific disorders, as guidance is available in other American College of Occupational and Environmental Medicine (ACOEM) Guidelines. Instead, it addresses a general approach to the evaluation and management of patients with chronic pain, while also including guidance for a few specific disorders (i.e., complex regional pain syndrome, fibromyalgia, neuropathic pain) not found elsewhere in the guidelines. This guideline also addresses psychological and behavioral aspects of chronic pain to a far greater degree than found in the other ACOEM guidelines. This is due to the major influences of psychological and behavioral issues in many chronic pain patients. (see Figure 1).

The objectives of the Chronic Pain Guideline include examinations of baseline status, diagnostic tests, imaging, physical activity, return to work, medications, physical therapy, injections, rehabilitation psychological evaluations, and behavioral treatment. The comparative effectiveness of various treatment options is addressed where research is available. It is recognized that there are differences in workers' compensation systems.[1] There also are regional differences in treatment approaches.[2-4] The Evidence-based Practice Chronic Pain Panel and the Research Team have complete editorial independence from the American College of Occupational and Environmental Medicine and Reed Group, which have not influenced the Guidelines. The literature is routinely monitored and evaluated

for quality publications that would modify this guidance. The guideline is planned to be comprehensively updated at least every five years, or more frequently should evidence require it. The health questions for chronic pain disorders (including for complex regional pain syndrome, neuropathic pain, fibromyalgia, chronic persistent pain, chronic pain syndrome) addressed by this guideline include the following:

- What evidence supports the initial assessment and diagnostic approach?
- What red flags signify potentially serious underlying condition(s)?
- What diagnostic approaches and special studies are needed to clarify the clinical pathology?
- What initial treatment approaches have evidence of efficacy?
- What is the evidence of work-relatedness for various diagnoses?
- What modified duty, activity prescriptions, and/or limitations are effective and recommended?
- When is it acceptable to return the individual to work?
- When initial treatment options fail, what evidence supports other interventions?
- When and for what conditions are injections and other invasive procedures recommended?
- When and for what conditions is surgery recommended?
- What management options are recommended for delayed recovery?
- What evidence of efficacy is available for psychological and behavioral interventions for chronic pain conditions?

A detailed methodology document used for guideline development including evidence selection, scoring, incorporation of cost considerations,[5, 6] and formulation of recommendations is available online as a full-length document[7] and also summarized elsewhere.[8, 9] All evidence garnered from 7 databases was included in this guideline (Medline, EBM Online, Cochrane, TRIP, CINAHL, EMBASE, PEDro). Comprehensive searches for evidence were performed with both PubMed and Google Scholar up through 2016 to help assure complete capture. There was no limit on year of publication. Search terms are listed with each table of evidence. Guidance was developed with sufficient detail to facilitate assessment of compliance[5] and auditing/monitoring.[6] Alternative options to manage conditions are provided.

This guideline has undergone extensive external peer review. All AGREE II [6], IOM [5] [5], AMSTAR , and GRADE criteria are adhered to in this guideline. In accordance with the IOM's Trustworthy Guidelines, detailed records are kept, including responses to external peer reviewers.[5]

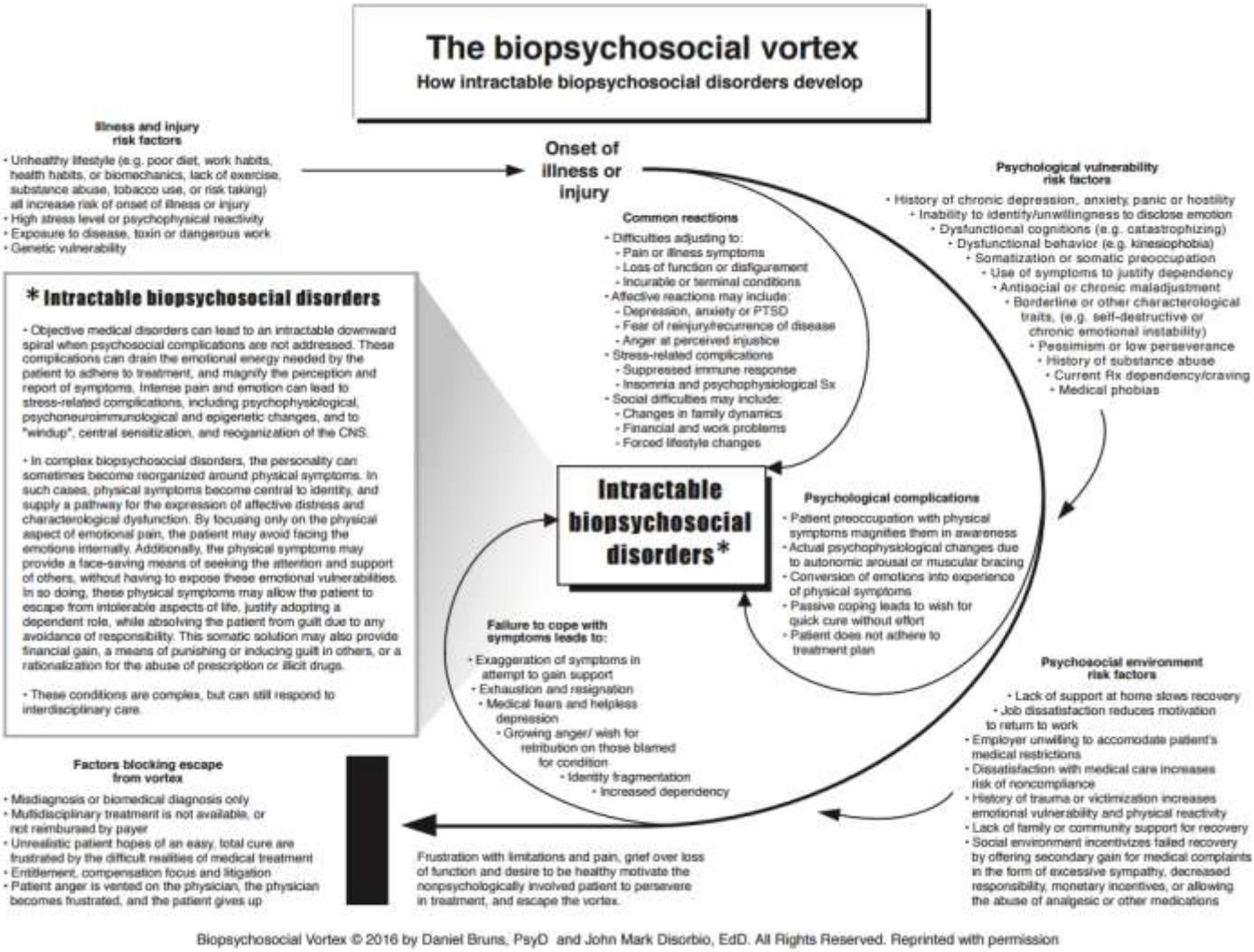

Figure 1. The biopsychosocial vortex: How intractable biopsychosocial disorders develop. Reprinted with permission from Daniel Bruns, PsyD, and John Mark Disorbio, EdD.[1]

[1]The biopsychosocial model was initially conceived as a new model for medicine, which could provide a means of integrating the biological aspects disease and illness with its psychological and social aspects. It was hoped that this new model could provide, "…a blueprint for research, a framework for teaching, and a design for action in the real world of health care" (Engel, 1977)(p 129). Since its inception, the biopsychosocial model has spawned a wealth of research and practice models, and is the model adapted into this guideline. At the same time, the biopsychosocial model itself is often presented as vague philosophical abstraction. One attempt to define the biopsychosocial model with greater specificity is the Vortex Paradigm (D. Bruns & Disorbio, 2009, 2014; D Bruns & Disorbio, 2015). This paradigm conceptualizes intractable medical conditions such as chronic pain as being precipitated by the cumulative effect of biological, psychological and social risk factors. The Vortex Paradigm suggests numerous falsifiable hypotheses that can be tested by multivariate methods. In a manner similar to the way heart disease can be predicted by a multivariate equation that includes cholesterol, age, blood pressure, diabetes, genetics etc., the Vortex Paradigm would predict that return to function following injury can be predicted by a multivariate equation that includes biological severity, depression, catastrophizing, drug abuse, personality disorder, job dissatisfaction, childhood trauma, secondary gain, etc.

In the clinical setting, the Vortex Paradigm would posit that biological, psychological and social variables may all contribute to the onset of an injury or illness. Once present, a significant biological condition may have direct psychological and social consequences, and these may interact with the patient's pre-existing biological, psychological and social strengths and vulnerabilities. As the level of biopsychosocial risk factors increases, the risk of decompensation (a "downward spiral") into an intractable chronic condition increases. When the patient presents to the physician, all of these variables are present, and a treatment plan should be developed regarding how to either actively treat or manage these concerns, to prevent them from delaying recovery.

Impact

Pain, whether acute or chronic (defined as pain of more than 3 months' duration), is the most prevalent health condition found among the U.S. workforce and the costliest in terms of lost productivity. Sixty-

four percent (64%) of adults over age 30 experience chronic pain.[13] An estimated 20% of American adults (42 million people) report that pain or physical discomfort disrupts their sleep a few nights a week or more. (American Academy of Pain Medicine 2016). Health care expenditures for back and neck pain alone have risen to more than $80 billion a year in the United States, increasing 50% in 8 years without evidence of improved health status.[14] About 25 million U.S. adults are reporting chronic pain daily at an estimated economic cost of $560-635 billion per year (Dubois 2014, Gaskin 2012, American Academy of Pain Medicine 2016). The economic burden combines the medical costs of pain care and the economic costs related to disability days, lost wages, and productivity (American Academy of Pain Medicine 2016). In addition to the costs of lost productivity, an estimated $64 billion in lost costs is largely invisible to employers because employees are continuing to work with limitations caused by pain, which reduces job performance. This is called "presenteeism."[15-23] People with chronic pain have the equivalent of 4.9 more days of presenteeism than people without chronic pain [24].

Overview

Recommendations on assessing and treating adults with chronic pain are presented herein. Topics include the initial assessment and diagnosis of patients with chronic pain, identification of red flags that may suggest the presence of a serious underlying medical condition, initial clinical evaluation, management, diagnostic considerations, and special studies to identify clinical pathology, work-relatedness, modified duty and activity, rehabilitative strategies, return to work, psychological evaluation, behavioral treatments, and further management considerations including delayed recovery. This guideline does not address cancer pain management.

Summary of Recommendations and Evidence

The following is a general summary of the recommendations contained in this guideline:

The Evidence-based Practice Chronic Pain Panel's recommendations are based on critically appraised higher quality research evidence and on expert consensus observing First Principles when higher quality evidence was unavailable or inconsistent (https://www.acoem.org/guidelines_methodology.aspx). The reader is cautioned to utilize the more detailed indications, specific appropriate diagnoses, temporal sequencing, preceding testing or conservative treatment, and contraindications that are elaborated in more detail for each test or treatment in the body of this Guideline in using these recommendations in clinical practice or medical management. These recommendations are not simple "yes/no" criteria.

All ACOEM guidelines include analyses of numerous interventions, whether or not FDA-approved. For non-FDA-approved interventions, recommendations are based on the available evidence; however, this is not an endorsement of their use. In addition, many of the medications recommended are utilized off-label. (For example, anti-epileptic agents have been used off-label since the 1960s to treat chronic pain.)

Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient-Recommended (Consensus-based), "I" Level

- Insufficient-No Recommendation (Consensus-based), “I” Level
- Insufficient-Not Recommended (Consensus-based), “I” Level
- Not Recommended, “C” Level
- Moderately Not Recommended, “B” Level
- Strongly Not Recommended, “A” Level

Basic Principles and Definitions

Active Therapy: The term “active therapy” is commonly used to describe treatment that requires the patient to assume an active role in rehabilitative treatment. Although there is no one specific treatment defined by this term, it most commonly includes therapeutic exercises, particularly aerobic activities and muscle reconditioning (weight lifting or resistance training).[25] Some also include active stretching, and treatment with psychological, social and/or educational components requiring active participation from the patient in this category.[26]

Active Exercise Therapy: Therapy that typically consists of cardiovascular training and strengthening of muscles,[27, 28] though it may also include progressive or occasional active stretching, especially in those with substantially reduced ranges of motion. Active exercise therapy is used as a primary treatment for chronic pain, is frequently initiated in the course of treating acute and subacute pain, and is a primary treatment after various surgeries. The goal of therapeutic active exercise is to improve function.[27] The word “active” is used to differentiate individualized exercise programs designed to address and rehabilitate specific functional, anatomic or physiologic deficits from passive treatment modalities or from forms of “exercise” that require very little effort or investment on the part of the patient or provider.

Acute Pain: Pain of 1 month or less duration. Pain lasting >1 month but <3 months is termed “subacute”.

Central Pain: Pain that is due to a lesion or other abnormality that is located in the central nervous system. Examples of disorders in this category include tumors, strokes and traumatic brain injury (TBI) sequelae.

Central Sensitization and Central Sensitivity Syndromes: Central sensitization is considered a condition of the central nervous system that produces and maintains a chronic pain state. While the exact mechanism(s) is(are) not known, the entity is believed to involve an up-regulation from a normal state of perceptions of pain. Patients may have increased sensitivity to pain, thus experiencing as painful something that normal individuals would not generally consider painful (e.g., touch, pressure), also known as allodynia. They also usually experience more pain than usual to a mildly painful stimulus (hyperalgesia). The prototypical diseases for central sensitization have been generally considered to be post-stroke and spinal cord injury. Other diseases commonly associated with central sensitivity include fibromyalgia, traumatic brain injury, and multiple sclerosis.

Chronic Pain: Pain categorized purely based on duration is defined as chronic when lasting at least 3 months. This may be divided into chronic malignant pain and chronic non-malignant pain, although evidence of meaningful differences between those 2 categories is negligible. Yet, chronic pain is much more complex.

Pain is known to be associated with sensory, affective, cognitive, social and other processes [1-4]. The pain sensory system itself is organized into two parts, often called first and second pain. A-ð nerve fibers conduct first pain via the neospinalthalamic tract to the somatosensory cortex, and provide information about pain location and quality. In contrast, unmyelinated C fibers conduct second pain via the paleospinalthalamic tract, and provide information about pain intensity. Second pain is more closely associated with emotion and memory neural systems than it is with sensory systems [5-7].

As a patient's condition transitions through the acute, subacute and chronic phases, the central nervous system is reorganized. The temporal summation of second pain produces a sensitization or "windup" of the spinal cord [8], and the connections between the brain regions involved in pain perception, emotion, arousal, and judgment are changed by persistent pain [9]. These changes cause the CNS's "pain neuromatrix" to become sensitized to pain.[1-4] This CNS reorganization is also associated with changes in the volume of brain areas [10], decreased grey matter in the prefrontal cortex [10], and the brain appearing to age more rapidly [11]. As pain continues over time, the CNS remodels itself so that pain becomes less closely associated with sensation, and more closely associated with arousal, emotion, memory and beliefs [7,12]. Because of these CNS processes, the physician should be aware that as the patient enters the subacute phase, it becomes increasingly important to consider the psychosocial context of the disorder being treated, including the patient's social circumstances, arousal level, emotional state, and beliefs about the disorder. However, behavioral complications and physiological changes associated with chronicity and central sensitization may also be present in the acute phase, and within hours of the initial injury.[13]

Chronic Non-malignant Pain (CNMP): Pain lasting over 3 months that is not due to neoplasms, cancers, or tumors. It is also referred to as chronic non-cancer pain (CNCP). It is a subcategory of all chronic pain which may be further subdivided into the subcategories of chronic persistent pain and chronic pain syndrome. The former predominantly refers to pain duration with the latter indicating that additional features such as limited functional status, vocational status, and/or significant psychological features are present.

Chronic Pain Syndrome: Pain over 3 months duration with additional features such as limited functional status, vocational status, and/or significant psychological features are present.

Delayed Recovery: An increase in the period of time prior to returning to work or usual activities compared with the length of time expected based on reasonable expectations, severity of disorder, age, and treatments provided.

Factitious Illness: A mental disorder wherein the patient either falsifies or self-induces symptoms of illness. It is thought to involve both conscious and non-conscious factors. The primary drive is thought to be assuming the role of being a patient or being sick. By definition it is not occupational.

Functional Capacity Evaluation (FCE): A comprehensive battery of performance-based tests used to assess an individual's ability for work and ADL.[29] An FCE may be done to identify an individual's ability to perform specific job tasks associated with a job (job-specific FCE), or his/her ability to perform physical activities associated with any job (general FCE). The term "capacity" used in an FCE may be

misleading in cases where there appears to be functional limitations, since an FCE generally measures performance rather than capacity, thus understatements of true capacity are likely whereas overstatements are less likely. There is also significant variation in study quality, generally reflecting, at least in part, both the experience and overall orientation of the provider performing the study.

Functional Improvement (especially Objective Evidence): Evaluation of the patient prior to the initiation of treatment should include documentation regarding objective physical findings and current functional abilities both at home and at work. This should include a clear statement regarding what objective or functional goals are to be achieved through the use of treatment. These measures should be tracked during treatment and evidence of progress towards meeting these functional goals should be sought. Examples of documentation supporting improved function would be increased physical capabilities including job specific activities, return to work, return from off-duty-status to modified duty, performance of exercise goals, participation in progressive physical therapy, and other activities of daily living. Validated tool(s), such as the Modified Oswestry Questionnaire and Roland-Morris Disability Questionnaire may also help track progress, although they are subjective. Objective improvements in strength or aerobic capacity may be physical examination correlates of improved function.

Functional Restoration: The term functional restoration is often used for a variant of interdisciplinary pain alleviation or at least amelioration characterized by objective measurement of physical function, intensive graded exercise and multi-modal pain/disability management with both psychological and case management features.[30-36] The term has become popular as a philosophy and an approach to medical care and rehabilitation. In that sense, the term refers to a blend of various techniques (both physical and psychosocial) for evaluating and treating the chronic non-malignant pain patient, particularly in the workers' compensation setting.

Hyperalgesia: Increased or markedly painful response to a stimulus which is normally painful (e.g., light pinprick leads to extreme and prolonged pain). This is in contrast to **allodynia**, pain due to a stimulus which does not normally provoke pain (e.g., light touch causes pain).

Major Depressive Disorder: Major Depressive Disorder is a psychiatric condition that may or may not be related to chronic pain as it is common without pain. However, there is a high occurrence rate with chronic pain. Co-morbid psychiatric conditions including major depressive disorder may interfere with treatment as well as outcomes.

Malignant Pain: Pain associated with cancer, or treatment effects of cancer is commonly termed malignant pain. This pain should be distinguished from non-malignant pain or chronic non-malignant pain.

Malingering: The conscious feigning, manufacturing, or exaggeration of symptoms for purposes of secondary gain (e.g., monetary, avoidance of work, obtaining drugs). Though relatively uncommon, malingering is likely substantially more prevalent in occupational settings than other contexts due to monetary and other incentives. It is usually suggested, in part, through atypical clinical presentations, psychological evaluation, or discrepancies with surveillance or videotaping.[37] Malingering is not considered a mental disorder.

Neuralgia: Pain that is thought to be nerve related and is present in the distribution of a nerve or nerve root.

Neuritis: Neuritis technically describes an inflammation of a nerve(s). In practice it is often inaccurately used to label any pain thought to be nerve-related, regardless of whether or not there is an inflammatory process.

Neurogenic Pain: Pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system.

Neuropathic Pain: Pain caused by abnormal function of the nervous system due to injury or disease. There is generally no relationship between end-organ damage and pain perception as is thought to be present in nociceptive pain. Although an affected individual perceives pain as emanating from some bodily structure (e.g., the distal lower extremity in sciatica), the pathophysiologic basis for the pain is believed to be an abnormality in the functioning of the central or peripheral nervous system, rather than an abnormality in the location where the pain is perceived. Neuropathic pain can be due to a lesion in the central nervous system, as is seen in post-stroke pain or thalamic pain, (central neuropathic pain) or due to lesions in the peripheral nervous system. Postherpetic neuralgia, painful neuropathies (e.g., diabetes mellitus), and what was previously referred to as causalgia (CRPS II) are all examples of conditions characterized by peripheral neuropathic pain.

Neuropathy: A disturbance of function or pathological change in a nerve. This is called a mononeuropathy if involving one nerve. If diffuse and bilateral, it is called a peripheral or polyneuropathy.

Nociceptive Pain: Pain that arises through the normal activation of pain pathways. In the acute stage, it serves as a protective mechanism to alerting the individual to the presence of potentially damaging stimuli. Stimuli are transduced at the injury site with chemical, mechanical, and thermal stimuli all eliciting responses in specific subsets of neurons. These stimuli result in increased firing rates in pain-specific neurons with *transmission* of neural signals resulting ultimately in pain *perception* at the cortical level. Once the inciting stimulus is removed and healing has occurred, nociceptive pain typically resolves. While nociceptive pain can be somatic (carried along the sensory fibers) or visceral (transmitted through the autonomic nervous system), most injuries lead to somatic pain.

Nocebo Effect: The opposite of placebo effect, occurring when the patient believes that exposure to treatment, activity, or event may be harmful and leads to adverse effects or results in less benefit than expected.

Outcome measure for Psychological Testing. In contrast to screening measures or psychological tests, it is preferable if an outcome measure contains only changeable “state” items, not unchanging “fixed” items (e.g. a history of suicide attempt is an indiction of depressive vulnerability, but treatment cannot change this fixed historical fact). An outcome measure is scored using an ipsative method which compares the patient to him/herself (e.g. is your score today better than when you started?). Outcome measures may assess physical functioning, quality of life, psychological states, or satisfaction with care. An example of outcome measures are the PROMIS tests.

Pain Behavior: Verbal and non-verbal actions (e.g., grimacing, groaning, limping, using pain relieving or support devices, requesting pain medications, etc.) which communicate the concept of pain to others.

Pain Disorder: An ICD-10-CM (American Version) diagnosis that is assigned to patients with chronic pain. Pain Disorder has two subtypes. The first, F45.41 "Pain disorder associated with psychological factors" is a psychological or stress-related condition that is neither precipitated by nor associated with any objective pathophysiology (e.g. chronic tension headache). The second, F45.42 "Pain disorder with related psychological factors" is a biopsychosocial diagnosis where pain is believed to be associated with both medical and psychological diagnoses (e.g. herniated lumbar disc and depression). Note that the ICD-10-CM diagnosis of Pain Disorder is more closely associated with DSM-IV-TR concepts than it is with DSM 5, and that the DSM 5 diagnosis of "Somatic Symptom Disorder, Pain Predominant" has no equivalent in ICD-10-CM. While the DSM-IV-TR diagnosis of Pain Disorder was diagnosed in part by "medically unexplained symptoms," this is now believed to be a misleading criterion. When F45.42 is diagnosed, the code for the associated medical diagnosis should also be provided.

Pain Documentation: Pain is most commonly assessed via patient report using numeric or visual analog scales. It cannot yet be measured objectively. Assessing the physiology of peripheral structures which may be involved in nociceptive or other afferent transmission is often not germane to the clinical issue of pain. While tools such as functional MRI have been used experimentally,[41] imaging studies and other diagnostic procedures that "document" the existence of centrally mediated or experienced chronic pain, and/or identify increased or decreased activity in specific CNS structures in association with chronic pain states, have not yet been shown to be clinically relevant.

Passive Modality: Various types of provider-given treatments in which the patient is passive and not required to take an active part in the treatment. These treatments include medication, injection, surgery, skilled non-medical therapies (such as massage, acupuncture, and manipulation), and various physical modalities such as hydrotherapy (whirlpools, hot tubs, spas, etc), ultrasound, TENS, other electrical therapies, heat, and cryotherapies.

Peripheral Pain: Pain that is due to pathology in a location other than in the central nervous system. This includes some examples of neuropathic pain (e.g., pain from an entrapment neuropathy) and all types of nociceptive pain (e.g., pain from muscle-tendon unit abnormalities).

Placebo Effect: A placebo effect is a beneficial effect that is not attributable to the "intervention" itself. This effect may be based on patient and provider belief(s) and/or expectation(s). This includes clinical improvement or benefit (which can be objective or purely subjective) seen when a patient's belief that a "sugar pill" or sham medication or treatment will help him or her get well, even when there is no reason to believe that any "true" or specific therapeutic effect has occurred.

Psychological tests. Psychological tests are part of the standard for assessing chronic pain, and are generally indicated by a positive psychological screening test or by other indications. The length of a psychological test is much longer than a typical screening test or outcome measure. They are usually multidimensional and have multiple validity scales. These tests are typically standardized with test results compared to norms which produce a percentile rank. Standardized tests are protected by test security (not posted on the internet, requiring a credentials check to obtain), and typically have a published peer review by the Buros Institute. These are interpreted by a psychologist and/or physician with appropriate training. A minimum of two standardized psychological tests specific to the reported concern, when possible, are generally required.

In contrast, brief nonstandardized psychological tools may be freely available (e.g., The Pain Catastrophizing Scale, the CES-D, the Pain Anxiety Symptom Scale, the Pain Self Efficacy Scale) and scoring keys for these scales are publicly available. The public nature of these scales increases the ease of manipulating the results if financial incentives are present. These tools do not have validity measures, and typically use cutoff scores rather than standardized scores with percentile ranks. These measures require less training to administer.

Screening tool. A screening tools is generally succinct, and may be as short as one or two questions. It is usually administered to either an entire population, or an entire cohort of patients with a given condition. The frequency is usually at least in the initial exam and/or once a year. The objective of most screening tests is optimization of sensitivity, but not specificity. A screening tool may be often administered by persons with minimal training.

Somatic Symptom Disorders: Somatic symptom and related disorders is a category of conditions described by the DSM5, and which was offered as an alternative to the ICD10 category of somatoform disorders. Somatic symptom disorders consist of somatic symptom disorder [confusingly the same name as the category], illness anxiety disorder, conversion disorder, psychological factors affecting other medical conditions and factitious disorder. Unlike somatoform disorders where unexplained medical symptoms were a central construct, somatic symptom disorders are thought to commonly co-occur with objective medical conditions.

Somatoform Disorders*:* A category of related mental disorders found in the ICD10 but not the DSM5, in which there are symptoms and complaints which are not medically explained. This group of disorders includes pain disorder, conversion disorder, somatization disorder, hypochondriasis, and body dysmorphic disorder. Pain disorder, which also falls into this category, may or may not be associated with a medical condition. With the exception of pain disorder, the somatoform disorders are infrequently encountered in association with a work injury and are not generally considered occupational disorders. However, they are prominent in the differential diagnosis for patients with chronic pain. Body dysmorphic disorder is sometimes found in chronic non-malignant pain patients with burn injuries or amputations. These diagnoses are important diagnostic considerations in the chronic pain population and are often difficult to detect without formal psychological evaluation and testing.

Skilled Non-medical Therapies: Treatment approaches that require extensive training and development of specific skills. These treatments include manipulation, mobilization, massage, and acupuncture.

Subacute Pain: Pain lasting 1 to 3 months.

Symptom Magnification: This is a term that commonly denotes conscious or unconscious increases in reported pain levels beyond those the patient is experiencing. This usually is accompanied by pain behaviors such as exaggerated impacts on gait, range of motion, strength and other functions.

Tender Points: Unusual tenderness on palpation at a tendon insertion or origin, muscle belly or over bone. Some examiners require palpation of a taut muscle band or knot to qualify as a tender point. The most widely used criteria are palpation of the area(s) involved with the thumb or forefinger, applying pressure (palpation) approximately equal to a force of 4 kilograms (blanching of the entire nail bed) with a requirement for the patient to acknowledge that the palpation is not merely a discomfort, but would be described as pain. Tender points are specific places on the body (18 specific points at 9 bilateral

locations) that are exceptionally sensitive to the palpation in patients with fibromyalgia, although the most common definition for fibromyalgia no longer requires tender points. Tender points are not limited to these locations and can occur anywhere in the musculature.

Trigger Points: Frequently used as a synonym for tender points, but is technically reserved for a subset of tender points in which there is elicitation of distal symptoms, usually accompanied with local symptoms, on palpation of the tender point. Trigger points are traditionally associated with myofascial pain, but few clinical trials differentiate these two conditions, thus the potential importance of this traditional distinction is unknown. (See Shoulder Disorders Guideline)

Visual Analog Scale (VAS): Measures a patient's reported level of pain, ranging from "no pain" to "worst pain" by indicating a mark on a line, frequently 10 cm long. The distance from the low end of the line to the patient's "x" is the pain score.

Initial Assessment

The clinician performing an initial evaluation of a patient with chronic pain has the particularly difficult task of ascertaining whether there is (are) other treatable, explanatory condition(s) present. Yet it is also critical to avoid over-testing which may result in increased morbidity (e.g. iatrogenic impairment) through either direct adverse effects of the tests themselves, or more likely through creating and contributing to a mind frame of endless searching for a potential lesion to be "cured." This tends to be most problematic with spine disorders (see e.g., Low Back Disorders Guideline).

Findings of the medical history and physical examination may alert the clinician to other pathology that can present with pain or some of the other constitutional symptoms with which the patient with chronic pain may present. Certain findings, referred to as red flags, raise suspicion of serious underlying medical conditions (see Table 1). Potentially serious disorders include infections, tumors, and systemic rheumatological disorders.

A careful, thorough history is required. The approach generally needs to be comprehensive, exploring all aspects of the physical complaints. A relevant review of symptoms is necessary. It is critical to evaluate psychological and social factors. Equally important is the evaluation of occupational and environmental functions, with particular emphases on psychological, physical and social barriers that may be addressed to limit the impacts of the condition. Significant efforts to acquire prior test results are preferential to obtaining new studies, as excessive testing tends to maintain foci on symptoms, searches for a "cure," and tends to increase obstacles to achieving a functional recovery. Screening instruments may be helpful especially to screen for psychological disorders.

Absent red flags, most patients with common forms of chronic non-malignant pain may be described as having one or more of the following conditions:

- Complex regional pain syndrome (CRPS): Type I and Type II;
- Neuropathic pain: central, peripheral, and radicular;
- Trigger points/myofascial pain (see Shoulder Disorders guideline);
- Tender points/fibromyalgia;

- Degenerative joint disease, including osteoarthrosis (see body part guidelines, specifically Hip and Groin Disorders, and Knee Disorders guidelines);
- Chronic spine pain (see Low Back Disorders, and Cervical and Thoracic Spine Disorders Guidelines)
- Chronic persistent pain;
- Chronic pain syndrome;
- Chronic lower abdominal/pelvic pain;
- Chronic non-specific pain syndrome; and/or
- Psychological disorders (most common are the affective disorders, anxiety, depression. Other disorders are also reported risks in some literature).

It should be noted that patients with chronic pain syndromes may have one or more of several psychological disorders. Depressive disorders are particularly prominent factors.

Red Flags

Physical evidence of an underlying medical or psychological problem that correlates with the medical history and test results may suggest a need for immediate consultation. A history of malignancy, infection, endocrinological or systemic disorder may suggest the possibility of an underlying serious condition. A medical history that suggests pathology originating in a location other than that originally injured may require investigations that would not appear to be related to the work injury but would nonetheless need to be performed (e.g., shoulder pain from gall bladder or cervical spine; joint complaints from rheumatological disorders). Psychosocial red flags include dangerousness to self or others, acute intoxication, psychosis, and homelessness [1440]. Evidence of risk factors for delayed recovery may also be of concern, and may be considered "yellow" flags [1440]. Table 1 focuses primarily on systemic conditions that may have been missed in a patient with complaints of chronic pain. However, if the person has no past history, then the professional should still evaluate, assess and query about current psychological issues due to the high co-morbidity rate with chronic pain.

Table 1. Red Flags for Potentially Serious Conditions Associated with Chronic Pain*

Disorder	Medical History	Physical Examination
Tumor and Neoplasia	Severe localized pain, often deep seated, non-radiating unrelenting boney pain History of cancer (at ***any*** point in a lifetime) Age >50 years Symptom consistent with disease in a specific organ system Cough Change in bowel habit, epigastric pain, early satiety Pain that worsens with use of specific body part Constitutional symptoms, such as recent unexplained weight loss, fatigue	Pallor, reduced blood pressure, diffuse weakness Tenderness over boney landmark(s) and percussion tenderness corresponding to pain complaints Decreased range of motion due to protective muscle spasm New mass or tenderness Abnormal pulmonary examination (rales, rhonchi, decreased breath sounds)

	Pain that continues at night or at rest Development of new symptoms at a distant site to the original complaint not readily explained by that original problem (e.g., development of cough in a patient with shoulder pain) Pain non-responsive to usually effective treatments (e.g., low back pain not responding to evidence-based treatment guidance)	New findings at a distant site to the original complaints
Infection	Constitutional symptoms, such as recent fever, chills, or unexplained weight loss Recent bacterial infection (e.g., urinary tract infection); IV drug abuse; diabetes mellitus; or immunosuppression (due to corticosteroids, transplant, or HIV) History of recurring infections treated with antibiotics (e.g., repeated urinary tract infections) Foreign travel with exposure potential Insect bites	Fever, tachycardia, tachypnea, hypotension Elevated white blood cell count (may be decreased in elderly, immunocompromised or sepsis) Shift in the WBC differential towards immature cells ("left shift") Abnormal urinalysis Abnormal body part examination (e.g., pulmonary) Tenderness over boney landmarks
Progressive Neurologic Deficit	Severe spine and/or extremity pain Progressive numbness or weakness Complaints of new clumsiness of gait or impairment of hand function	Significant and progressive dermatomal and/or myotomal (motor) involvement Evidence of cauda equina syndrome– urinary retention or bowel incontinence Hyper-reflexia or other evidence of myelopathy
Intracerebral Pressure Increase or Mass or Vascular Lesion	Persistent or variable headache present on awakening Episodic severe headache Subtle loss of coordination or balance Cognition or other mentation difficulties History of cerebrovascular accident, or stroke-like symptoms, including transient	Papilledema upon fundoscopic exam. Possible mild neurologic findings Possible mental status changes
Rheumatologic Disease	Diffuse arthralgias, either a/symmetrical Joint swelling and/or prolonged morning stiffness Skin changes, lesions, or ulcers Oral ulcers Gastrointestinal diseases Fatigue, malaise Subtle mental status changes	Polyarticular joint effusions (usually with warmth) Synovitis, joint tenderness Range of motion reductions X-ray abnormalities consistent with erosive or degenerative pathology Elevated sedimentation rate (ESR) or C-reactive protein (CRP) Hematuria, proteinuria

		Other specific abnormalities as appropriate (e.g., ANA, RF, anti-DNA, C3, anti-Ro, anti-La, oral ulcers, pulmonary abnormalities, ophthalmological involvement, dermal abnormalities)
Psychosocial	Suicidal ideation Violent ideation Psychosis Substance abuse/opioid dependence Homelessness	Positive signs on psychological screening/testing Patient interview

*This list is not meant to be comprehensive; it is a review of the most common suggestive historical and examination findings.

Absence of Red Flags

In the absence of red flags, the evaluation of the patient with chronic pain may progress as noted below. The evaluation is recommended to be centered on function, while not ignoring pain.

History

A focus on the potential for a treatable condition is mandatory for an initial evaluation of a patient with chronic pain. Nevertheless, it is recommended that the initial evaluation of patients with chronic pain start with a focus on function, both at work and home. This sets the focus on function that is essential for the vast majority of chronic pain patients, while maintaining a focus on confirmation that prior examiners did not miss a treatable disorder.

Collecting information about occupational history and patterns of daily living and interests assists in understanding patient priorities and targeted outcomes. Alertness to the patient responses is important, as there may be strong clues to the degree to which preoccupation with somatic complaints instead of a functional focus is present. Unprovoked responses frequently also provide powerful clues to activities the patient is interested in resuming that may ultimately provide the motivational tools to facilitate the patient's functional restoration. The provider should ask typical questions focused on pain symptoms. Current pain treatments, whether medical or non-medical, should be recorded. Past pain treatments should be reviewed with a careful discernment and documentation of meaningful, lasting functional improvements.

After the function-based and pain histories are obtained, the history should next include a thorough medical history, past medical history, medication history, surgical history, accident history, current psychological history, and past psychological history.

The primary treating provider, other health care professionals, and consultants should approach pain complaints as an integral element of each history and physical examination. Yet the primary focus should be on function, rather than pain to avoid an undue focus on pain and pain ratings. This includes assessing pain complaints relative to casual patient observations, the physical examination and observation of the patient's functions both while actively examined and ideally outside of the context of

the performance of a physical examination. Obtaining a history of functional activities from family members or friends may sometimes be useful.

Medical History Questionnaire

Asking the patient open-ended questions such as those below allows the provider to gauge the need for further discussion or specific inquiries to obtain more detailed information (see Appendix 3 for additional questions).

1. Functions on the Job:

- What is your job?
- What are your specific regular/modified duty job duties?
- How well do you function at work?
- How long do you spend performing each duty on a daily basis?
- Do you have assistance of other people or lifting devices?

Functions off-work Activities:

- What other activities (hobbies, workouts, sports) do you engage in? At home or elsewhere?
- How well do you function at home?
- Describe your current daily activities from awakening to bedtime. Do you go grocery shopping, prepare your own meals, and do yard work or laundry?
- Any heavy lifting? How? How often?

2. What are your symptoms? (How the patient acts when describing their symptoms may help ascertain the expression and meaning of pain to the patient. In particular, does she or he appear concerned or unconcerned relative to the signs of injury or illness? How much time does the patient spend describing the pain and in what detail – validating or acknowledging pain may reduce these behaviors and facilitate interventions.)

- When did your symptoms begin? Gradual vs. acute onset? If acute, what was the specific event?
- Where are the symptoms located?
- What activities make you worse or better?
- Do you have pain or stiffness?
- Do you have numbness or tingling?
- Do you have pain or other symptoms elsewhere?
- Have you lost control of your bowel or bladder?
- Do you have fever, night sweats, or weight loss?
- Are your symptoms constant or intermittent? What makes the problem worse or better?
- What is the day pattern to your pain? Better first getting out of bed in the morning, during the morning, mid-day, evening or while asleep? When is it worst? Do you have a problem sleeping? What position is most comfortable? Is there any pain with coughing, sneezing, deep breathing, or laughing?
- Have your symptoms changed since the time they began? How?
- How does having this pain affect your life?

3. How did the condition develop?

Past:

- Have you had similar episodes?
- Have you had previous testing or treatment? What treatment? What were the results? With whom? How long did it take to get back to work? To light duty? (Was recovery similarly delayed?)
- Did you receive a disability or impairment rating?
- Was recovery complete? (Did you receive a disability award?)

Cause:

- What do you think caused the problem?
- How do you think it is related to work?
- Were you doing anything at that time when your symptoms began? (It is important to obtain all information necessary to document the circumstances and biomechanical factors of injury to assist the patient and workers' compensation system in obtaining just compensation.)
- Did your symptoms begin gradually or suddenly? Did you notice the pain the day after the event?
- Did you have a slip, trip, fall, strike, twist, or jerk?
- For traumatic injuries: Was the area deformed? Did you lose any blood or have an open wound?

4. Discuss symptom limitations.

- How do these symptoms limit you?
- How long have your activities been limited?
- How long can you sit, stand, walk, and bend?
- Can you lift? How much weight (use items such as gallons of milk, groceries, etc. as examples)? How much can you push or pull?
- Are you working on your regular job? Modified duty?
- What activities do you perform in a typical day? Begin with waking in the morning and proceed to bedtime. What activities are you now unable to do? Why?
- Do you need to lie down or rest during the day?
- What activities at home do you need help with?

5. Assess treatments and how the responses may or may not have differed from expected outcomes.

- What treatments have you had?
- Did anything help decrease your symptoms? What and for how long?
- Exactly what treatment did you receive in physical therapy (detailed descriptions of all modalities and specific exercises used)? Did it help? How?
- Are you doing physical therapy exercises at home? How often do you perform them? When? Do you feel that they help? Please show me how you do them.

6. Are there other medical problems? For example:

- Osteoarthrosis, rheumatoid arthritis, or other arthritides

- Cardiovascular disease
- Pulmonary disease
- Gastrointestinal problems
- Diabetes mellitus
- Neurological disorders (including headaches)
- Psychophysiologic disorders (e.g., irritable bowel syndrome, chronic fatigue syndrome, sick building syndrome, muscle tension syndrome, and multiple chemical sensitivity)

7. Are there, and how many psychosocial "yellow flag" risk factors are present?
    a. Have you ever had anxiety?[1] Depression?[2]
    b. Have you ever had psychological, psychiatric or mental health evaluation, treatment or counseling? When? Concerning what issue(s)? For how long were you treated?
    c. Do you have any memory or concentration problems?
    d. Have you ever had a substance use problem? DUI? Blackouts? Detoxification?
    e. Have you ever used or are you now using marijuana?
    f. How much alcohol do you consume in an average day? Week?
    g. How many cups of coffee do you have a day? How many cups of tea? How many sodas? Caffeinated or decaf? What size is the beverage? How much chocolate do you eat each day?
    h. Tobacco use? Prior use? (packs a day for how many years)
    i. Do you take any other drugs? (current and prior use)
    j. How well do you sleep? How many hours of sleep do you get each night? Do you have any problems falling asleep? Do you have any problems staying asleep? Do you wake up early?

8. What is the occupational psychosocial context?
    a. If you had to take a job again, would you go back to your current job?
    b. Do you like your job?
    c. What is your relationship with your co-workers and supervisor and how do they treat you?
    d. How do you get along with your supervisor?
    e. How do you get along with your coworkers?

[1] Clinical presentations of anxiety vary widely. Common symptoms of anxiety include feeling nervous, tense, restless; trouble sleeping; early awakening and worrying about things; avoiding things that trigger nervous feelings; sensing impending danger, panic, or doom; fatigue; trouble concentrating; inexplicable gastrointestinal problems including nausea, constipation, diarrhea, abdominal pain, and irritable bowel syndrome. Physical manifestations may also occur and include palpitations, hyperventilation, sweating, trembling.

[2] Clinical presentations of depression vary. Common symptoms of depression include feeling down, sad, blue, hopeless, tearful; loss of interest in normally pleasurable activities; social withdrawal; sleep disturbance; fatigue; lack of energy; irritability; frustration; difficulty thinking and concentrating; memory problems; appetite changes, with weight gain or loss. Particularly with more severe presentations, other symptoms commonly occur, including feeling worthless; focusing on past problems and failures; suicidal thoughts; slowed thinking, speaking and body movements. Some patients experience symptoms of anxiety as well as depression.

f. How do your coworkers help you if you need it?
g. How does your supervisor help you if you need help?
h. Is your employer concerned about you?
i. What kinds of successes and difficulties were you having on the job before you got hurt?
j. Are you facing any disciplinary or performance action?

9. Is the worker encountering perceived problems with the ergonomics of the job or workstation?
    - What do you do for work/modified duty?
    - What are your work hours and breaks?
    - Do you rotate jobs?
    - What is the hardest part of the job for you to do with your injury? Why?
    - How much do you lift at work as a maximum? Usual lift?
    - How often do you do those tasks?
    - Describe work times, movement and breaks for sedentary jobs.

10. Assess whether there are problems at home/social life. Does the patient feel in control of most situations? Is there support?

    - How do your family members get along with each other?
    - How do they help and support you?
    - Does your family treat you differently now that you are in pain? Have your roles at home changed because of your injury?
    - How do your friends treat you differently?
    - Do you get increased symptoms when you are dealing with problems with your family and friends? How often? When? Why? Does stress change your symptoms?

11. Are there advocagenic (litigious) influences?

    - Do you have a workers' compensation claim for this injury?
    - Have you consulted anyone (union representative, etc.) about particular problems you may have experienced with your claim (not receiving benefits, etc.)?
    - Do you have additional insurance coverages such as short- or long-term disability?
    - Have you taken sick time for this problem?
    - Do you have a lawyer? Have you ever been involved in a prior lawsuit?
    - Do you have a worker's compensation claim, lawsuit or other legal action involving this pain problem?
    - Did you talk with your lawyer about what you should say at the clinic?

12. What are your expectations regarding your return to work and disability from this health problem?

13. What are your concerns about the potential for further injury as you recover?

14. What do you hope to accomplish during this visit?

As noted previously, many of these factors are operant during the acute and sub-acute phases of injury.

The **Stanford Five** (created by Dr. Sean Mackey of Stanford University) is an augmented set of medical history obtained by the clinician during the medical interview for patients with pain. The Stanford Five is designed to assess and present the pain experience as viewed from the patient's primary belief system. The following are the components of the Stanford Five:

- **Cause**: What tissue abnormalities the patient believes to be the cause of the current problem
- **Meaning**: The presence of any sinister beliefs related to the pain, in terms of tissue damages, that precludes activities
- **Impact**: What impact the primary problem has on the patient's life, including interference on vocational, social, recreational activities, and in general the patient's quality of life
- **Goals**: What the patient expects to achieve with further treatment
- **Treatment**: What the patient believes needs to be done now and in the future to help resolve the problem

Physical Examination

A well-performed physical examination is indicated for the evaluation of a patient with chronic pain, both by the treating provider and a consultant if one is utilized. Components of the physical examination should follow those of the relevant body part involved and will not be detailed in this section (see other ACOEM Guidelines). The examination of individuals with somatoform disorders is often indistinguishable from that of psychologically normal individuals. The threshold for psychological referral, including psychometric testing for this and other entities, should be quite low.

Observation of the patient is believed to be the most important aspect of the physical examination. It should begin at the start of the visit—or better still, through a report from the medical assistant who put the patient in an examining room. It should include an evaluation of the patient's ability to arise from a seated position (and other positional changes), gait in the hallway (e.g., for all lower extremity or spine complaints; examination rooms are too small to adequately observe gait), utilization of limbs for tasks, and facial expressions in the course of performing those functions. Synergistic and dys-synergistic history and physical examination findings should be sought and recorded.

Particularly in the setting of chronic pain, signs that are inconsistent with symptoms should be sought. These have been previously referred to as "nonorganic" signs and were developed for the evaluation of low back pain.[42, 43] (see Table 2). However, similar findings of overreaction and nonanatomic distributions of pain are believed to equally apply to the evaluations of all other body parts. It should be noted that positive results with these maneuvers are sometimes erroneously taken to be definitive of factitious illness and/or malingering. That may or may not be true. More commonly, it is believed that these may be positive when patients in pain subconsciously exhibit a need for further attention to the painful disorder or sometimes may represent psychological dysfunction. Their presence indicates the likely need for psychosocial evaluation, particularly when multiple signs are present in the context of significant delayed recovery.

Table 2. "Nonphysiologic" Physical Examination Signs [43]

Physical Examination Maneuver	Definition of Nonphysiologic Sign
1. Superficial tenderness	Discomfort on light palpation
2. Non-anatomic tenderness	Tenderness crossing anatomic boundaries
3. Axial loading	Pain elicited on pressing down on the occiput
4. Pain on simulated rotation	Pain or augmentation of pain on gentle rotation of the torso that does not rotate the lumbar spine
5. Distracted straight leg raise	Pain on straight leg raise when recumbent, but not when seated
6. Non-anatomic sensory complaints	Stocking/glove distributions of sensory changes
7. Non-physiological weakness	Cogwheeling, ratcheting or give-away weakness
8. Overreaction	Exaggerated response to stimulus, particularly if not reproduced when retested later

Adapted from Waddell G, McCulloch HA, Kummel E, Venner RM. Non-organic physical signs in low-back pain. *Spine*. 1980;5:117-25.

Numbers 1 and 2, 3 and 4, 6 and 7 were combined in the original criteria. As originally described, scores over 3 were felt to show high probability of symptom magnification or illness behaviors. Subsequently, even one sign was associated with greater morbidity in the acute LBP setting.[42]

In the chronic pain setting, it is frequently helpful to obtain measurements of the patient's capabilities in the clinic to then follow in subsequent clinic visits while the patient is undergoing rehabilitation services. These may include the following:

- Walking distance (observe in the hallway or outdoors and subsequently simultaneously interview the patient about their progress if a longer walking ability is demonstrated)
- Ability to climb stairs (walking to the nearest stairwell with the patient and observing capabilities)
- Dynamometer grip strength measurements
- Pinch strength
- Repeated toe raises (number able to perform)
- Distance of heel walking
- Squats (number)
- Sensory examination findings (e.g., monofilaments)
- Movement inconsistent with pain/injury problem while in exam room

This also moves the examiner from the role of a more passive observer to a more active team leader, including more informed decision making, such as in conjunction with therapists on exercise and other physical activity benchmarks. Active involvement of the provider is believed to be quite helpful to facilitate the patient's recovery.[44] The use of validated functional assessment tools to follow patient progress is another recommended approach.

Associated Factors, Risk Factors, and Work-Relatedness

A method for determination of work-relatedness is discussed in detail in the Work-Relatedness Guideline. Each disorder-specific ACOEM guideline has detailed discussions and evidence citations

regarding specific occupational disorders. Thus, this guideline will only briefly review a few additional chronic pain-specific issues.

Aside from a significant, discrete traumatic event (e.g., laceration; substantial slips, trips, or falls), much of what is classified as acute pain in the occupational setting is best modeled as a relatively sudden onset of pain, such as low back pain, in the context of a multifactorial disorder. The minority who sustain a significant traumatic event have workers' compensation claims that are largely noncontroversial. This applies to many cases of complex regional pain syndrome if the onset was due to a specific, discrete event at work.

Work-relatedness of specific disorders are discussed in those modules, including CRPS, Fibromyalgia, Chronic Persistent Pain, and Neuropathic Pain.

Chronic pain associated only with psychological disorders may be occupational, although most cases are not work-related. Factitious illness, malingering, conversion disorder, somatization disorder, hypochondriasis, and body dysmorphic disorder are all non-occupational conditions. Pain disorder, which also falls into the somatoform disorders category, may or may not be associated with a medical condition; thus, it may or may not be occupational depending on whether there is a clear occupational inciting event that caused the medical disorder.

Follow-up Visits

It is **Recommended (I)** that patients seeing a new healthcare provider or while still out of work for a work-related chronic pain disorders should have a follow-up visit every 1 to 2 weeks initially to evaluate the patient, initiate treatment(s) and/or adjust prior treatment regimen(s). Appointments should generally be time-contingent, i.e., scheduled as opposed to obtained secondary to changes in pain complaint. Those initial visits should include further focusing on function, obtaining more information from the patient, confirming that the history information is consistent, observing for injury/illness behaviors, confirming the diagnosis, and assessing the need for psychological referral and evaluation. The educational process of informing the patient about functional status and the need to engage in a functional rehabilitation program focusing on restorative exercises should be reinforced. These restorative exercise program components should be labeled the cornerstone of the medical management plan for the patient's pain. Other means of managing pain, including pharmaceuticals should be addressed. Initial visits for chronic pain should also include information to avoid bed rest, excessive rest or appliances. The provider should take care to answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery.

Subsequent follow-up is **Recommended (I)** to be less frequent, and tailored to the patient's needs. In cases where the patient is at work, fully functional and on minimal or steady-state maintenance NSAID medications, follow-up every 6 to 12 months is **Recommended (I)**. However, in the active rehabilitation phase for patients with CRPS, when constant encouragement is required to continue performing exercises, follow-ups weekly for as much as 2 or 3 months is **Recommended (I)** to remain in concert with physical therapy, occupational therapy, as well as to sustain a team-oriented focus on restoration and achievement of functional goals.

Diagnostic Approach to Chronic Pain

Chronic pain is considered by most providers to be best evaluated and treated as a disease.[45-50] Pain, defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage,"[51] can be a valuable guide to diagnosing and resolving illness or injury. It also can be a problem that interferes with activities of daily living (ADL) and instrumental activities of daily living (IADL). ADLs involve caring for oneself through dressing, grooming, feeding, etc., while IADLs involve functional activities such as using the telephone, shopping, housekeeping, food preparation, transportation outside the home, responsibility for taking medications, and the ability to handle finances.

The "biopsychosocial model" which emphasizes the need to account for the unique interactions between biological, psychological, and social factors in order to better understand health and illness, is now commonly utilized to explain and manage chronic pain since the traditional medical model of acute injury resulting in pain and tissue damage does not explain chronic pain syndromes (see Figure 1).[52, 53] Central nervous system (CNS) factors may explain the experience of pain in the absence of tissue damage or after healing has taken place.[54] Genetic factors may also play roles in the perception and responses to pain.[55, 56] Psychological and social factors are also involved in the perception and interpretation of pain symptoms and their effects on home and work life.[53, 57] Psychological factors are prominent in the management of patients with chronic pain, profoundly influence the individual's ability to modulate pain and distress, and are better managed after earlier identification.

Pain occurs in the context of each person's life situation, affecting work and social functioning as well as the ability or willingness to be active. In settings of acute pain (e.g., trauma), brief inactivity may reduce pain. However, in subacute to chronic problems, inactivity either results in no improvement or more pain, delays recovery, and is accompanied by deconditioning. Thus, increased activity is indicated for essentially every chronic condition associated with persistent pain. For select, acute pain conditions, reduced activity limitations to facilitate recovery may be appropriate. Yet, in the chronic context, recovery is usually dependent on performing those specific activities that may elicit the pain on a gradually increased basis in order to return to normal function. A substantial clinical difficulty is timing and facilitating the transition from acute pain and activity limitations to chronic pain and graded increases in activities. Determining how soon to recommend increased activity levels is problematic, although there is increasing consensus to implement increased activity levels earlier and earlier in the acute and subacute phases to prevent delayed recovery and the development of chronic pain syndromes.

Development of chronic pain syndromes may be complicated by the practitioner's lack of a quality curricular background in chronic pain management, a field long under-represented in educational programs. Provider foci on acute pain management particularly with reduced activity levels and passive treatments tends to foster delayed recovery and further development of chronic pain syndromes. Chronic pain differs from acute pain and a different treatment approach is needed. When health care providers focus on pathology rather than on the individual, the person with pain is often ill-served and turns from a person into a patient. The task in successful chronic pain management is to turn the patient back into a person.

Prevention of Chronic Pain Syndrome

There is an important therapeutic window for preventing chronic non-malignant or non-cancer pain problems from becoming a chronic pain syndrome (e.g., a functioning patient successfully coping with LBP through exercise and the judicious use of medication vs. a patient seeking treatment after treatment in a protracted quest to eliminate all pain). The timing of the critical window of opportunity to prevent the development of a chronic pain syndrome is unclear, but many believe this window is identifiable in the acute pain phase by recognizing factors for delayed recovery and there is consensus that it should be well recognized no later than the early subacute pain phase. If psychosocial risk factors are not identified and addressed in the subacute phase, there is an increased risk of enduring changes in the central nervous system which contribute to central sensitization and to the transition to a chronic condition.

Pain may or may not be well localized, yet it is frequently compounded by the severity of motivational, affective, cognitive, and behavioral overlay that is often a frustrating aspect of chronic pain.

Signs and Symptoms of Patients at Risk for Chronic Pain

More intense pain complaints; Extreme pain
Widespread pain. Non-anatomic pain
Overprotective/fear of exercise & very sedentary (e.g. kinesiophobia or fear avoidance))
Diffuse symptoms of distress/somatization (e.g. fatigue, anhedonia, appetite disturbance, weight change, poor concentration, nervousness)
Pain associated with depression, anxiety or anger, or with marked absence of any emotionality (alexithymia)
Moderate or severe sleep disturbance
Over-reliance on habit forming medications
No treatment helps, or only helps a little and for a short period of time. Pain never changes
Higher disability profiles[3]
Dysfunctional pain cognitions
Moderate to major difficulties with functioning or disability
Little physical and functional progress
Catastrophizing. Dysfunctional coping strategies
Emotional characteristics of chronic pain
Behavioral characteristics of chronic pain
Dysfunctional movements and patterns contributing to chronicity of pain, including:
Antalgic gait
Abnormal postures
Guarding

[3] Disability profile is a term commonly used to project the likelihood of disability. It has little relationship with physical injury or diagnosis. Instead, it is heavily driven by psychosocial health, psychological disorders, coping skills, resilience, etc.

If the focus successfully shifts from pain complaints to function and movement patterns are normalized, symptoms usually diminish and function increases markedly. Normalization is usually achieved through the following:

- Combination of changing emphasis on the desired outcomes (function)
- Reducing emphasis on subjective complaints (pain). However, if a subjective complaint is symptomatic of distress, that should be addressed and treated so the patient acquires and actively uses self-soothing skills.
- Increasing active therapeutic interventions
- Normalizing movement patterns
- Reducing passive interventions
- Addressing psychosocial factors sympathetically
- Acknowledging that psychological conditions occur frequently with pain disorders

The patient's level of education, cultural background, literacy, health literacy, and language background should be considered for their potential as barriers to progress. Reducing barriers to effective treatment may also help prevent the development of a chronic pain syndrome.

The keys are to promptly recognize this transitional period (when the patient begins to deviate from the expected recovery trajectory for his or her complaint, illness, or injury) and to institute rehabilitative or appropriate pain management techniques (e.g., institution of active therapies with fear avoidance belief training). Inability to make progress on these issues necessitates an early referral (e.g., experienced secondary or tertiary pain provider and psychologist) as the patient with chronic pain requires significantly different interventions than does the acute pain patient. While this sometimes places a strain on the time and skill of the treating provider, the provider is usually the most influential person in the patient's recovery, and his or her appreciation of and attending to these factors as valid and important clinical issues, is often key to successful resolution of delayed recovery and prevention of a chronic pain syndrome in an acute or subacute patient.

Before pain becomes chronic, there is an important therapeutic window for preventive interventions. During this transitional period, patients may present with some or all of the emotional and behavioral characteristics that are seen with chronic pain, but their pain is still potentially explainable with reference to tissue damage. It is important to recognize when the patient begins to deviate from the expected recovery trajectory for his or her complaint, illness, or injury, and to institute rehabilitative or appropriate pain management techniques or make a timely referral. For many patients, psychological or multidisciplinary evaluations may help, but the treating provider is still the most influential practitioner involved in the patient's recovery. The treater's understanding of these issues and attending to them as valid and important clinical issues is often key to successful resolution of either delayed recovery in a "pre-chronic patient" or effective treatment of a chronic pain syndrome.

Palliate or Rehabilitate

A related untoward outcome from the failure of successful restoration of normal function during the initial phases of treatment is the decision to make palliation the main focus of subsequent interventions.

To palliate rather than rehabilitate is a profound clinical, ethical, and medico-economic decision that should not be taken lightly or be based on unfounded dogma. While a patient's complaints of pain should be acknowledged, both patient and provider should remain focused on the ultimate goal of rehabilitation leading to optimal functional recovery rather than on continued health care utilization. Early identification and appropriate management of the patient exhibiting signs of delayed recovery is believed to decrease the likelihood that he or she will go on to develop chronic pain.

This guideline focuses primarily on chronic pain evaluation and treatment. Complete pain relief is clearly a highly desirable endpoint, especially in acute pain states, yet it is usually unattainable in patients with chronic pain. Evidence also suggests that factors other than the nature of the injury are primary determinants of disability. Pain treatment should emphasize functional restoration and pain relief. Emphasizing only pain relief may reinforce negative psychological, environmental, and dependent psychosocial factors that predispose progression to chronic pain states and addiction(s). In chronic pain states, emphasis on functional restoration should focus on improving function while reducing pain or limiting flare-ups to manageable levels. In those settings, the pursuit of an anatomic antecedent pain generator is counter-productive to achieving optimal functional outcomes. Patient education is also an important component to achieve the goals, as without the patient joining the treatment team, progress is typically very slow and the goals may not be achieved.

Pain that cannot be adequately explained by specific physical findings raises many questions: When does acute pain become chronic? Is the diagnosis correct? Is there a second diagnosis? Are changes in the patient's central nervous system creating pain hypersensitivity? What else is going on in the patient's life, either at home or at work, which may be aggravating his or her pain or reinforcing pain or illness behavior? How can such pain problems be articulated to a system that is based on labels and coding? How can that concept of pain be put into a medicolegal context when dealing with workers' compensation issues? Does the current treatment improve function? What role should patients play in promoting optimal function in everyday living and enabling meaningful family, workplace, and social relationships? What is the patient's emotional response to pain? The following discussion sheds light on these questions and suggests an interdisciplinary model to address the multiple components of the patient's pain problem. It also addresses specific recommendations for several specific, as well as general categories of chronic pain disorders.

Evaluation and Diagnostic Issues

- In all cases, the body part that is injured should be carefully evaluated with a history, physical examination, and focused diagnostic testing (see specific guideline guidance). A complete physical is recommended, since pain can be referred from remote organs or anatomical segments (e.g., gallbladder to shoulder or hip joint to knee pain).

- Treatment "failures" are often due to lack of follow-through on initial recommendations for return to function, and can be identified through the patient history.

- The first focus of the initial chronic pain examination or consultation of a patient with chronic pain should be the detection of conditions that are readily remediable. This search also includes "red flags," "yellow flags," and searches for potential alternative conditions.

- Judicious use of diagnostic testing for the initial chronic pain examination or consultation to search for a specific, remediable cause may be appropriate.
- Pain is a subjective experience for which there is no unequivocally objective measure. However, verbal reports of pain can be assessed with regard to compatibility with objective medical findings, and the patient's behavior. This includes consistency of findings with those expected for the condition, consistency of findings during observations within one appointment, and between appointments.
- Repeated diagnostic testing in the absence of indicators for a specifically targeted, remediable cause is not indicated as it focuses the patient on finding an anatomic abnormality, rather than focusing on maintaining and increasing functional outcomes.
- In cases where the chronic pain condition is associated with a substantial functional compromise and the cause is not apparent, a consultation to confirm the diagnosis and management plan is often appropriate and reassuring to the patient and family. Pain medicine specialists, musculoskeletal disorders experts and other experts in the body part injured as well as behavioral health experts (e.g., pain psychologist, psychiatrist) are all potential consultants for these patients, particularly for purposes of diagnostic confirmation.

Patient Education Issues

- Providers should reassure the patient that chronic pain is common, has a good prognosis in the absence of specific disorders, and does not cause (or have to cause) serious debility. Providers who provide encouragement that chronic pain is common and manageable are believed to have better outcomes with more effective use of resources,[58] including having more satisfied patients and fewer patients on disability. Reassurance should be tailored to the individual's unique perceptions and lifestyle.[59]
- Providers should address kinesiophobia (fear avoidance), or the fear or anxiety of movement. While activity is feared, it is an important therapeutic target because lack of activity reinforces debility. Patients should be encouraged to work with skilled therapists who can address fear of pain/movement to facilitate recovery and/or functional restoration.
- Patients should be encouraged to maintain as high a level of function at work and resume ADLs and IADLs. [60][61]
- Rest, bed rest, and disuse of body parts are not recommended for the management of chronic pain conditions as they cause further disability rather than assist in returning the patient to a functional status. The patient may need education to explain these common misconceptions and to address the accompanying fears that are frequently present.
- If the patient has been accurately diagnosed and adequately treated, a continuing focus on pain ratings and symptoms is counterproductive. Treatment must emphasize increasing function and supplementing the functional restoration plan with appropriate, judicious use of medications and other modalities.

- The patient's education level and cultural background should be considered, including possible language barriers.

Occupational Issues

- All patients should be encouraged to return to normal activity or work as soon as possible. Modified duty is most appropriately utilized when the job demands substantially exceed the patient's capabilities. For those patients on modified or light duty, a plan to return to normal job activities should be specified.
- Nonphysical factors (such as psychosocial, workplace, or socioeconomic problems) should be particularly addressed in cases of delayed recovery or delayed return to work.
- Patients should be encouraged to accept responsibility and learn necessary coping skills for managing their recovery rather than expecting the provider to supply an easy or complete "cure." Taking an active role in the recovery process is paramount if the person with pain is to return to work. This will promote using activity rather than pain as a guide, and it will make the treatment goal of return to occupational and non-occupational activities more obvious.
- Participatory ergonomics and return to work programs may assist in identifying job attributes that may be perceived barriers to a successful return to work.

Appliances and Skilled Nonmedical Therapies

- Slings, splints, and other appliances are contraindicated in managing chronic pain in the absence of focal neurological or structural deficits as they may reinforce pain and illness behaviors.
- Ice, heat, ultrasound, and other similar modalities are rarely indicated for chronic pain especially in the clinical setting. Heat and ice may be considered as a part of home-based self-care if their use provides the patient with temporary relief of symptoms, though the provider should be aware that these may also reinforce pain and illness behaviors in persons with chronic nonmalignant pain.
- There is no evidence to support prolonged and repetitive use of skilled non-medical therapies (massage, electrical therapies, manipulation, acupuncture, etc.). In the absence of documentation of functional improvement, they are not indicated in managing patients with chronic pain. These interventions tend to draw attention towards numbers of appointments and adding or trying more passive modalities, instead of focusing on and benchmarking increases in activity and exercise levels. Their use may be briefly indicated in conjunction with the introduction of an active conditioning program that includes both aerobic and strengthening components for treatment of referred patients found to have significant debility and deconditioning.
- Judicious short-term use of skilled, non-medical therapies may be indicated for significant exacerbations of underlying chronic pain conditions when there has been documented improvement following such treatments. Such exacerbations may be analogous to acute pain episodes; however, in the patient with chronic pain, such exacerbations are also believed to entail risk of sliding into reduced functional status. Providers who recommend these therapeutic approaches should be aware that they may detrimentally draw the focus away from increasing

function and reinforce pain behavior and disability. A transition back to active treatment modalities and self-care should be reinforced to the patient at that first visit to establish clear expectations.

Exercise Issues

- Graded exercises to assist in achieving a return to maximal function are indicated. Aerobic and strengthening exercises appear most helpful for the rehabilitation of most chronic pain conditions.
- Stretching or flexibility exercises may be important components to treat some patient's injuries. They are important when there is a significant reduction in range of motion and where restoration of range of motion is required to enable engagement in strengthening and functional activities. In general, stretching exercises can be taught by therapists, but should be performed by patients, repeatedly with limited numbers of repetitions to achieve most rapid gains in flexibility. However, where there is either minimal or no reduction in range of motion, strengthening and aerobic exercise should be emphasized.

Medications

- Although there is considerable overlap between types of pain, the provider should seek to identify whether chronic non-malignant pain is due to a specific diagnosis and/or thought to be *primarily* nociceptive, neuropathic, or of unclear etiology. Treatment options for these divergent types of commonly encountered pain have some differences. When evidence clearly indicates that specific medications are particularly effective in managing a given diagnosis or type of pain, they should be used preferentially. When the response to a medication has been suboptimal, consideration should be given to discontinuing it either before or immediately after adding a different agent.
- If an intervention is ineffective, it is better to stop it and try a different intervention (e.g., rather than switch to a different NSAID, consider a change in exercises, and/or a different class of medications).
- Opioid use in the setting of chronic, non-malignant, or neuropathic pain is controversial (see Opioids Guideline).
- Use of opioids in patients with chronic pain should be reserved for those with improved functional outcomes attributable to their use, in the context of an overall approach to pain management that also includes non-opioid analgesics, adjuvant therapies, psychological support, and active treatments (e.g., exercise).

Injection and Infusion Therapies

- While injection and infusion therapies are widely used in the management of patients with chronic pain, there is little high-quality research demonstrating efficacy and no evidence of long-term pain relief or objective functional increases. Hence, while they may have an occasional role in the management of carefully selected patients, their indiscriminant use is not recommended.
- When the decision is made to employ injection or infusion therapies as an adjunct to patient care, the goal should be to use the temporary decrease in pain to reduce use of opioids, encourage performance of exercises and increase functional activities. Documentation of objective,

quantifiable benefit as a consequence of their use must be provided, and repeated interventions in the absence of this documentation would not be warranted.

Psychological and Behavioral Issues

- Significant psychological factors are nearly always present as etiologic influences and/or sequelae when pain of nonmalignant origin becomes chronic as per the biopsychosocial model (see Basic Principles). Evaluation and management of these factors by the primary treating provider is recommended. When recovery is excessively delayed or psychological/psychiatric treatment by the primary provider is ineffective, consideration should be given to obtaining a comprehensive psychological evaluation. Fear of further injury (i.e., fear avoidant belief or "kinesiophobia") or missing a diagnosis also needs to be addressed if the person with pain is to progress.

- The presence of psychological factors has been significantly associated with the development of pain chronicity in patients with musculoskeletal disorders [62][63]. Pre-morbid depression is a particularly notable risk factor for the evolution of chronic back pain complaints, which along with related psychosocial factors, often supersede various mechanical or medical factors.[64-85] However, MDD can and frequently does occur with a pain condition.

- It is often difficult for many clinicians to focus a pain treatment plan primarily on psychological issues, other than mental health professionals. Frequently, a patient may become defensive and deny that there is any psychological component. Mind and body can be blended together in a comprehensive pain program by ensuring the person with pain understands the connection. Even compliance with some of the off-label medications such as anti-depressants and anti-convulsants need to be carefully explained to ensure the patient clearly understands the multiple purposes of these treatments.

- Fear-avoidance models are also thought to contribute to explaining chronic pain and kinesiophobia.[86, 87] There typically are strong fears of further injury and damage. Also many patients fear having more pain—so addressing pain-related anxiety is important because it impedes rehabilitation. The theoretical premise is that pain-related fear (beliefs that pain is a sign of damage or harm to the body, and activities that might cause pain should be avoided) has a significant impact on disability and adjustment. However, it is the *learned* behavior restrictions which are reinforced by activity avoidance and for which "fear" is the subjective covariate that are likely etiologic. Rehabilitative strategies which make use of this concept and try to diminish dysfunctional avoidant behaviors that are inconsistent with objectively definable risk of harm tend to be more successful.

Other Issues

- The majority of those with chronic pain do not seek professional health care, and often control symptoms with simple modalities such as over-the-counter medications, a heating pad, exercise and other remedies. Even those who have had complicated courses (e.g., complex treatment, litigation, etc.) may reach a state of self-management and coping with pain. The empowerment of patients to independently manage their pain as early as possible should be strongly encouraged.

- Patients using over-the-counter medications for management of chronic pain should be educated and assessed for potential adverse effects, as those are most likely to occur among chronic medication users, especially with other risk factors such as age. There also are potential interactions between herbal and prescription treatments.

- Patient involvement in litigation or workers' compensation claims has been shown to be associated with poorer clinical outcomes, including delayed return to work, poorer satisfaction with treatment, and worse surgical outcomes.[88-97] There are marked differences from state to state with regards to whether patients typically retain attorneys for worker's compensation. Accordingly, whether a patient is involved in litigation over workers' compensation may or may not raise concerns about possible advocagenic influences on the patient's clinical course and prognosis. It is recommended that these local cultural factors be taken into account when attempting to discern potential influences on pain complaints, treatment responsiveness, and disability.

Psychological Issues

Pain-related fear is believed to contribute to pain and disability in several ways. While pain avoidance is natural, persons who acknowledge greater pain-related fear tend to avoid more situations than would be normal due to their belief that they may cause pain. Research also suggests that compared with others, these persons tend to focus on the amount of pain experienced during functional activity, leading to greater activity avoidance. In this fashion, pain-related fear and associated avoidance of activity are believed to contribute to disability independently of pain itself. This may lead to greater physical deconditioning, but also has been shown to be related to musculoskeletal abnormalities such as muscle guarding while bending, which in turn may directly contribute to pain behavior.[98-100]

Pain-related fear is significantly related to greater perceived disability, even when controlling for biomedical factors, demographic variables, and self-reported pain.[101-103] Gradually exposing patients to fearful activities as pathway to reduce or extinguish pain-related fear can be a powerful intervention for chronic pain. A decline in pain-related fear may reduce pain hypervigilance, resulting in a decline in reported pain intensity. Reductions in pain-related fear may be partially responsible for improvement in functional restoration programs as the program duration may be too short for meaningful physiological effects of exercise.[104]

The Biopsychosocial Model

The biopsychosocial model (BPS) views health as including optimism, social support, good coping, positive mood, motivation, and work ethic. The model views disorders such as chronic pain as the result of a dynamic interaction among physiologic, psychological, and social factors which perpetuate and may worsen the clinical presentation. Thus, the model explains some patients with severe injuries who have profound perseverance, motivation and superior recovery.

The BPS model focuses on both disease and illness, with disease defined as disruption of specific body structures or organ systems by an objectively definable biological event that leads to anatomical, pathological, or physiological changes. In contrast, illness is generally defined as a subjective experience or self-attribution that a disease is present, thus referring to how a sick individual and members of his or her family live with and respond to symptoms and disability. The BPS model recognizes that each

individual experiences pain uniquely, with a range of psychological and socioeconomic factors interacting with physical pathology to modulate a patient's report of symptoms and subsequent disability. The relationship between psychological factors and the development of chronic pain reflects the differences between individuals in both the emotional reactions associated with the perception of pain and the risk of physical harm during the acute phase, as well as the psychological reactions that occur when pain becomes more chronic. The latter reactions take various forms depending upon both premorbid or pre-existing psychosocial characteristics and the patient's socioeconomic and/or environmental milieu. The role of afferent and efferent feedback between biological and psychological systems is emphasized, as the pain due to injury is seen as disrupting the body's homeostatic regulation systems, producing "stress" that ultimately leads to increased activity in the hypothalamopituitary axis (HPA).[52]

These in turn are hypothesized to lead to neurochemical changes at the central level, with the central nervous system altered by chronic pain to increase sensitivity to incoming impulses that amplify pain.[54, 105] Activation is believed to lead to further physiological changes, the extent of which are hypothesized to depend on intrinsic (genetic and physiological) and extrinsic factors, which exacerbate and perpetuate a syndrome in which the experience of pain increases despite a lack of objective reasons for this to occur.

The most widely accepted and evidenced model for explicating the biopsychosocial perspective provides a common language for describing and assessing continuing pain complaints.[106-108] Pain is defined as a noxious sensory AND emotional experience. Pain is known to have components designated as nociception, pain, suffering, emotional and pain behavior. The perception of pain may occur in the absence of nociception (or neuropathy) and vice versa. Therefore, the complaint of pain should be considered valid regardless of the assessed tissue pathology. Challenges to the complaint (other than forensic) tend to exacerbate the problem for many patients with chronic pain with resulting increases in pain complaints and pain behaviors.

Suffering is a set of negative affective responses which tends to be associated with the experience of pain. It may be produced by pain, but it may also be influenced by numerous psychosocial factors. These are often manifested by irritability, anger, frustration, personal losses, helplessness, social isolation, and various stress related states. Suffering may occur in the absence of "pain," but it is often described in such terms. In clinical contexts, it is often more necessary to assess how the patient is suffering than to attempt to relieve the pain. *Pain behavior* may be defined as "any response or set of responses which communicates the concept of pain to another person." The concept may be broadened to the notion of *illness behavior,* which involves other health related complaints and responses. Pain behaviors may be considered symptoms in acute pain presentations. However, they are also produced by suffering; and over time they may come under control of various psychosocial or learning influences.[109-112] There is a common misconception that such behaviors may represent consciously "exaggerated" or "magnified" symptoms. This is not possible to assess directly, and such conceptions are often pejorative. Pain or illness behaviors may evolve in persons with chronic pain secondary to a wide range of psychosocial antecedents and learning or conditioning influences. The implication that such behavior indicates a specific psychological etiology or necessitates a psychiatric diagnosis may not be justified. Since there is

no known relationship between nociception, pain, and pain behavior when a condition becomes chronic,[51] such behavior should be conceptualized as a clinical finding.[113] Pain behavior is also not equivalent to "secondary gain." While the latter is generally based on presumptively seeking reward or other desirable consequences of an injury, pain behavior may be learned or conditioned, shaped, and maintained by subtle reinforcement in persons about whom such psychological inferences may be inappropriate and where significant suffering or antecedent psychosocial problems are not noted. There is evidence that persons with chronic non-malignant pain may be uniquely sensitive to operant and classical (Pavlovian) conditioning in the learning of pain responses.[114-116] Still, chronic non-malignant pain may foster psychosocial and behavioral dysfunction, as well as magnify pain. The distinctions between these situations become important in the development of interventions to address them.

In persons with chronic non-malignant pain, many permutations of these concepts are possible. For example, significant and disabling pain and illness behavior may evolve and become a clinical problem, even in the absence of clinically meaningful nociception, pain, or suffering. Pain behavior may be noted in the presence of nociception or neuropathy, but the patient may not be suffering in clinically meaningful ways and may not be disabled. Other persons may be suffering, but their pain complaints may be a minor part of their problems. It is important to view the patient in this context and evaluate and treat these components appropriately, which requires a more complex evaluation and treatment plan than required for the patient with uncomplicated acute pain.

Diagnostic Criteria

If the patient does not have red flags for serious conditions, the provider should determine the diagnosis. The criteria presented in Table 3 follow the clinical thought process, from the mechanism of illness or injury, to unique symptoms and signs of a particular disorder and, finally, to test results (if any tests are needed to guide treatment at this stage). The ICD coding system assigns codes based upon pathophysiologic mechanisms. Specific ICD codes are frequently required for reimbursement for medical services. However, for at least 90% of LBP cases, the ICD codes utilized are overly specific. The pathophysiologic correlates for lumbar sprain and strain, for example, have not been determined. It is also difficult to match specific diagnostic ICD codes to the clinical presentation in many patients with chronic pain, especially initially.

Table 3. Diagnostic Criteria for Non-red Flag Conditions*

Probable Diagnosis or Injury	Symptoms	Signs	Tests and Results
Chronic Persistent Pain	Pain for 12 plus hours out of 24, or pain limiting specific activities (sleep, mood, or appetite disturbances may be present)	None, other than specific for a discrete entity (e.g., osteoarthrosis)	Diagnostic tests if targeting the specific body part and there is a potential for meaningful intervention
Neuropathic Pain	Burning, lancinating, independent of activity; weakness	May have normal examination or may have abnormalities that include muscle weakness, sensibility decrements, stretch	EMG/NCS Glucose tolerance testing, fasting glucose and/or hemoglobin A1c if concerns about diabetes mellitus

		reflex abnormalities, neurotrophic skin changes	Possible testing for alcohol (e.g., MCV, GGTP, hepatic enzymes) Rheumatological panels, ESR if concerns about those disorders
Central*	Highly variable findings depending on location and extent of injury Burning pain perceived peripherally in region of CNS insult	Highly variable findings depending on mechanism, extent of injury (may range from no objective findings to paralysis) Neurotrophic skin changes usually affecting ipsilateral upper and lower limb and maybe contralateral face	Brain MRI (occasionally spinal MRI) Somatosensory evoked potential studies – not indicated for radicular lesions but diagnostic for myelopathic injury/diseases EMG unlikely to be helpful, but often will be abnormal depending on location and extent of insult(s)
Peripheral	Burning pain in distal limbs (may have weakness)	Usually normal; may have symmetrical neurotrophic skin changes	EMG/NCS, blood studies (glucose, ESR, hepatic enzymes, MCV, rheumatological panels)
Radicular	Radiating, lancinating, burning pain Reduced sensibility along dermatomal distribution	Myotomal weakness Reduced stretch reflexes	MRI, EMG/NCS correlate with pain distribution, sensory and/or muscle/reflex deficits; for lumbar, positive straight leg raising present; for cervical, positive provocative maneuvers present
Complex Regional Pain Syndrome	Pain quality is similar to that described for "neuropathic," but involves a distal limb and extends beyond the distribution of a single peripheral nerve and is particularly severe	Asymmetrical use of extremities, swelling (or atrophy), mottling, temperature abnormalities, sudomotor findings, hair/nail/skin findings	Temperature discrepancy between limbs Bone scan $\geq$6 months after onset shows reduced uptake in affected extremity followed by increased radiotracer retention in peri-articular metaphyses of distal limb 3 hours later; 6 months after onset typical demineralization in long bones adjacent to joints distally on affected side Sweat studies
Trigger Points/ Myofascial Pain (See guideline on Shoulder Disorders)	Non-radiating, usually unilateral pain most commonly periscapular (generally unilateral and in body part subjected to injury)	Muscle taut band or knot with referred pain on palpation Palpation reproduces patient pain Absence of widespread tender points	None Occasionally, rheumatological testing is helpful to demonstrate an alternative disorder
Tender Points/ Fibromyalgia*	Widespread non-radiating pain often with prior or current depression, other affective disorders, and/or other psychological issues; fatigue often present	Absence of "objective" findings on exam. Numerous largely symmetrical tender points were a prior diagnostic requirement. Tender point(s) in muscle nevertheless are often present, which when compressed reproduce patient's pain	No inflammatory markers in blood studies; normal MRI, EMG, x-rays; generally no antecedent physical trauma
Chronic Pain Syndrome**	Enduring or recurring pain persisting longer than typical for an associated condition	Marked alteration in behavior with frequent depression or anxiety	Psychological evaluation (including diagnostic testing as indicated) may be useful

	Inadequate response to appropriate care Marked restriction in daily activities Excessive medication use and frequent use of medical services Excessive dependence on health providers, spouse and/or family; withdrawal from social milieu, i.e., work or other social contacts	Significant, reliable impairment of functional status inadequately explained by physical findings Evidence of possible psychological dysfunction such as anxiety, fear-avoidance, depression or significant pain or illness behaviors (may have "deconditioning" or poor aerobic endurance), passive-dependence	

*Chronic pain is defined as at least 3 months duration in this guideline.

**Non-occupational conditions included for completeness.

Adapted from AMA *Guides to Impairment Rating*, 6th edition[117] and Sanders et al. Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients. *Pain Prac*. 2005;5(4), 303-15.[118]

Testing Procedures

Diagnostic testing considerations are defined by the clinical entity and body part being investigated. Testing commonly used for the identification of other disorders is often required to assure that other diagnoses are not present. This should not be considered as justification for ordering tests indiscriminately. Tests should instead, be ordered if there is a reasonable probability that the diagnosis is present. Sometimes, the threshold for ordering a test is lower if the adverse effects from missing the diagnosis are considerable (see other guidelines for guidance on diagnostic testing for specific disorders). Imaging studies can identify abnormalities such as edema, demineralization, or osteoporosis that are consistent with one of the diagnoses associated with chronic pain, but mostly these are non-specific findings. There are different lines of clinical investigation of potentially useful technologies that purportedly assist in objectively diagnosing someone as suffering from, or being limited by "pain," or in localizing specific areas of the central nervous system that may influence, or be affected by, a patient's pain. Evaluations of the evidence for the use of many of these are provided in each section of this and the other ACOEM Guidelines (e.g., see Low Back Disorders; Cervical and Thoracic Spine Disorders; Hand, Wrist and Forearm Disorders; and Shoulder Disorders Guidelines).

Management Approach

This section is a general approach to treatment, not specific to diagnoses covered in other ACOEM Guidelines.

Initial Care

In general, interventions for treating pain should be time-limited and functional goal-oriented. Persons returning to work and life functions sooner after injury tend to have the best outcomes. Persons with equivalent diagnoses who are out of work for 3 months have worse return-to-work outcomes than those out 1 month, while those away for 1 year do worse than those out 6 months. Thus, there is a strong basis to return to a functional status sooner than later, including to work.

As noted previously (see Medical History), identification of psychosocial issues should be a major aspect of the initial evaluation or consultation for a new patient with chronic pain. A few of these issues include current or past mental health issues, family, friends, co-workers, supervisor relationships and support,

and drug-related issues. The mere denial of problems with (or history of) alcohol, illicit drug usage on initial examination is generally insufficient, as they are of significant prevalence in patients with chronic pain. There should thus be a focus upon approaching and ruling out substance abuse disorders and psychosocial issues which goes beyond the typical exam questions. Queries should also seek out chronic fatigue syndrome and irritable bowel syndrome as these disorders are reportedly associated with chronic pain syndromes[119-123] along with numerous other "functional somatic syndromes."[44]

While there are clinical systems that may elucidate risk factors for delayed recovery,[124-126] a comprehensive history and physical will generally identify at-risk individuals, after which referral to a psychologist or pain specialist can be considered if further evaluation and management of risk factors for the development of a chronic pain syndrome is desired. Referral to a psychologist or psychiatrist experienced in pain evaluation is often appropriate, especially when the pain is ill-defined, not well explained by anatomic or physiological abnormalities, associated with disability in excess of what would be expected based upon objective findings, or depression or anxiety are present. An additional consideration in the initial care of the patient with chronic pain is whether a multidisciplinary approach should be instituted to minimize disability and maximize function. This is described later in this document.

The following is a short outline followed by summaries of each specific disorder that is addressed in this guideline.

- Identify remediable generators of nociception or neuropathy (e.g., aggressive treatment of diabetes for diabetic neuropathy; aggressive rehabilitation exercises for CRPS).
- When there is no *readily resolvable* pain generator, the focus should be on functional restoration.
- Treatments should be individualized, taking into account co-morbidities and preferences.
- Address co-morbid mental health conditions with appropriate behavioral modification or medications.
- Medications or other treatments that have not been of clear benefit with an adequate trial should be discontinued prior to institution of alternative options. Treatments that are of some benefit should be continued while alternatives are weighed and checked to attain a reasonable chronic pain modulation (as a partial control is better than none in this population) to prevent them from seeking potentially detrimental treatment schemes. Medication effectiveness and adverse effects should be reviewed regularly with the patient and well documented in the medical record.
- Interventions with the potential for serious adverse effects should be employed if pain reduction and functional improvement will reasonably outweigh potential harms to the patient. Such interventions should be preceded by an adequate trial of conservative care. However, there are times when judicious interventional or medication therapy may be more appropriate than other strategies with potential to reduce pain and overall costs.

Treatment of most chronic pain conditions consists of a combination of therapies and interventions. Physical and psychosocial aspects should be considered when developing a treatment plan to suit the

patient's needs, reduce their pain, and improve their function. Most importantly, the patient must actively participate in the treatment plan. This often requires substantial and continued patient educational efforts. Guidance is available to assist with this approach.[127]

Activities and Activity Alteration

The overwhelming theme in the management of most patients with chronic pain is to keep them as physically active as possible.[128] There is no reason to avoid using the affected body part even in severe cases. All patients require advancement of activity levels and education because inactivity is detrimental despite the temporary relief of symptoms that often accompanies it. It is ironic that acute pain from an acute injury (not an acute manifestation of disease) may at times be successfully treated through a reduction in activity (e.g., casting a fractured extremity), yet subacute and chronic pain are best treated in exactly the opposite manner. In the late acute phase of subacute and chronic pain, the patient is generally best treated by performing gradually increased or graded activities to incrementally regain a fully functional status (i.e., usually requiring tolerating pain with each graded increase in occupational and non-occupational activity). The inability of some patients and providers to understand this transition and its major implications is believed to be one of the reasons that chronic pain conditions are so costly.

Because chronic pain conditions are so heterogeneous, it is not possible to give precise activity limitations. In general, patients with mild symptoms should be encouraged to perform all activities as normally as possible. They likely will require education and exercises. Those with moderate symptoms may or may not be able to work. If not, they should be in a therapy program 3 to 5 days a week, including daily home exercises, and gradually advancing activity levels outside of work within a program that targets return to work and meaningful productivity as a main treatment goal. Transition into the workplace is often useful for patients with chronic pain who are not working, particularly those with severe problems. Such transitioning usually requires careful coordination between the patient, treatment team, supervisor and co-workers. It may involve beginning on a modified duty job for 2 hours a day, then gradually advancing job physical requirements and/or length of time on the job until the worker is back to work full time. This process may take many weeks for those more severely affected, but is usually a highly effective method to both provide treatment and actively rehabilitate the patient with chronic pain.

Precise numbers of physical and occupational therapy appointments are not possible to specify due to the complexities of diagnosis, severity of the condition, degree of debility and individual factors involving ability to tolerate and exercise through pain. The key questions involve the documentation of ongoing, progressive, objective functional gains (e.g., return to work status, reducing work limitations, more repetitions of a rehabilitative exercise, walking further, etc.). As long as there is meaningful functional progress, additional therapy appointments are warranted until a plateau in function is reached. In general, prescribing therapy appointments for chronic pain patients and post-operative patients in increments of 5-8 appointments and then reassessing for functional gain prior to further prescriptions of additional appointments is recommended. A common approach is to gradually length time between visits. These approaches also allow for the development and implementation of a home

exercise program. A similar process for other appointments (e.g., manipulation, acupuncture) is also recommended regarding documentation of functional gain.

In general, activities causing a *significant* increase in symptoms should be reviewed with the patient and modifications advised when appropriate. Home and work activities may require at least temporary modification. It is now believed to be quite important to emphasize that an increase in pain does not represent or document damage. Instead, an increase in short-term pain as a result of increased activity levels in patients with chronic pain is actually believed to be normal and not detrimental to recovery. While the patient is being treated for a chronic pain syndrome, activities that do not aggravate symptoms should nearly always be maintained, and exercises to prevent debilitation due to inactivity should be advised. Aerobic exercise may be beneficial as a part of a therapeutic management technique that includes strengthening exercises as the cornerstone for management of patients with chronic pain (see Exercise). Stretching and flexibility exercises are particularly required where there is a significant limitation in range of motion and sometimes must precede strengthening exercises depending on the severity of the deficits. When range of motion is not significantly reduced, stretching exercises appear to be of much less importance than strengthening and aerobic exercises; in those settings, stretching exercises may be counterproductive as patients frequently do these 'easier' exercises and then skip or curtail the core rehabilitative exercises. The patient should be informed that activities might temporarily increase symptoms but that such exacerbations are normal.

Work Activities

Work activity modification is an important part of many treatment regimens. Advice on how to avoid substantially aggravating activities that at least temporarily increase pain includes a review of work duties to decide whether or not modifications can be accomplished without employer notification and to determine whether modified duty is appropriate and available. Making every attempt to maintain patients at the maximal levels of activity, including work activities, is strongly recommended as in their best interest, particularly among patients with chronic pain in whom debility is so commonly seen.

The analysis of work ability requires an assessment of "risk," "capacity," and "tolerance." Risk refers to what a patient can do, but should not do, due to the substantial risk of significant harm, considering probability and severity of potential adverse events. Providers impose work restrictions based on estimates of risk. Capacity refers to what a patient is physically capable of doing, as measured by concepts such as range of motion, exercise ability in metabolic equivalents (METs), etc. Tolerance for chronic symptoms like back pain is the basis for a patient (not a provider) to decide whether the rewards of work are worth the cost of the symptoms. Details of this assessment methodology have been described.[129]

The first step in determining whether work activity modifications are required usually involves a discussion with the patient regarding whether he/she has control over the job tasks. In such cases where the worker can, for example, get assistance from someone else to lift a box of parts to assemble, and can alternate sitting and standing as needed, there may be no requirement to write any restrictions even if the pain is limiting. Assessment of work activities and potential for modifications may also be facilitated by a worksite visit and analysis by a health care provider with appropriate training (e.g.,

experienced occupational therapist, physical therapist, occupational medicine physician, and/or ergonomist).

Work modifications should be tailored taking into account two main factors: 1) the job physical requirements; and 2) the safety of the tasks, in consideration of the diagnosed condition, age, and relevant biomechanical limitations. Sometimes it is necessary to write limitations or prescribe activity levels that are above what the patient feels he/she can do, particularly when the patient feels that complete rest or similar non-activity is advisable. In such cases, the provider should be careful to not overly restrict the patient, as it is clearly not in his or her best interest, and education about the pain problem and the need to remain active should be provided.

Common limitations involve modifying the weight of objects lifted, degree of stereotypical activity allowed (low, medium, high), frequency of lifts, and posture, all while taking into account the patient's capabilities. As noted above, there are many variables that must be incorporated into prescriptions of physical activities, thus they require individualization. There are not quality studies of restrictions, thus these are clinical judgments. For *severe* cases of chronic pain syndrome involving an upper extremity, frequent initial limitations for occupational and non-occupational activities might potentially include:

- Working 2 hours a day;
- No lifting over 5 pounds; and
- No highly repetitive or high force activities (e.g., push/pull) involving the affected hand.

For severe chronic pain syndrome involving a lower extremity or the spine, frequent initial limitations for occupational and non-occupational activities might potentially include:

- Working 2 hours a day;
- No lifting over 10 pounds; and
- Alternate sitting and standing as needed.

These work and home activity guidelines are generally reassessed every week in the early rehabilitation process with graded increases in activity recommended so that patients with a severe chronic pain syndrome evolve off modified duty in generally not more than 16 weeks. The amount of weight handled or force used with the hand can be progressively increased. Providers should also be advised that some workplaces provide health care or physical or occupational therapy on-site and this may further facilitate the rehabilitation process.

It is best to communicate early in the treatment that limitations will be progressively reduced as the patient progresses. Experienced providers communicate the intended changes in restrictions for the coming week (similar to forecasting increases in exercise program components) at the current visit to reduce the element of surprise and help actively facilitate the patient's most important elements of an active, functional restoration program. Tailoring of restrictions is required in nearly all patients with chronic pain as there is great variability in symptoms and dysfunction. The employer should also be consulted while developing strategies to expedite and support integration of the patient into the workplace.

The provider can assist patients and employers in explaining that:

- The patients usually have increased pain performing almost any function in the early rehabilitation timeframe, even if "light" duty;
- Increases in pain do not equate to injury for patients with chronic pain;
- Increases in symptoms should be heard with a sympathetic ear and the factors which are associated with significant increases in pain should be addressed;
- Any restrictions are intended to allow for time to build activity tolerance through exercise; and
- Where appropriate, it may be helpful to mention to the patient that this rehabilitative plan will also help him/her to regain normal non-occupational life functions.

Every attempt should be made to maintain the patient at maximal levels of activity, including work activities, as it is in the patient's best short term, as well as long term interest. *Work activity limitations should be written whether the employer is perceived to have modified duty available or not. Written activity limitations guidance communicates the status of the patient, and also gives the patient information on what he/she should or should not do at home.* Table 4 provides recommendations on activity modification and duration of absence from work for CPS. These guidelines are intended for patients without comorbidity or complicating factors, including serious prior injuries. They are targets to provide a guide from the perspective of physiologic recovery.

Table 4. Guidelines for Modification of Work Activities and Disability Duration

DISORDER	ACTIVITY MODIFICATIONS AND ACCOMMODATION	RECOMMENDED TARGET FOR DISABILITY DURATION*	
		Modified Duty Available	**Modified Duty Not Available**
Complex Regional Pain Syndrome (includes Types I and II)	Use extremity as normally as possible. Avoid aggravating activities involving extremity (e.g., forceful prolonged use, heavy lifting, walking or standing). Advance activities as soon as possible for better outcomes. Must be strongly individualized based on the severity of CRPS.	Mild 0-30 days Moderate 30-60 days Severe 60-90 days	Mild 0-30 days Moderate 60-90 days Severe 90-180 days
Peripheral Neuropathy	Generally no limitations required. For severe peripheral neuropathy, modifications may be needed to avoid significantly aggravating exposures (e.g., highly repeated forceful use of hand in distal upper extremity peripheral neuropathy).	Mild 0 days Moderate 0-7 days Severe 7-14 days	Mild 0-3 days Moderate 3-7 days Severe 7-21 days
Tender Points/ Fibromyalgia	Ideally, no limitations. May need graded increase in activity levels to regain normal function if significantly debilitated.	Activity limitations should be avoided.	Activity limitations should be avoided.

*Mild, moderate, and severe are defined by the degree to which the condition affects ADLs; e.g., mild involves little to no impairment in the impact on the patient's ability to perform ADLs, while severe involves marked impairment in the ability to perform ADLs. The provider should make these determinations based on the presumed impairment specifically due to the

underlying condition, noting that reported limitations in ADLs are often a function of psychological and occupational factors, which are typical in chronic pain. Where suspected, they should be ruled out or explicated in the process of determining what actual disability duration is warranted based on the specific underlying condition.

Disability durations are primarily consensus from the Evidence-based Practice Chronic Pain Panel. Disability durations also incorporate data used with permission from Reed Group, Ltd. Reed P. *The Medical Disability Advisor. Workplace Guidelines for Disability Duration, 5th Edition*. 2005. Westminster, Colorado: Reed Group, Ltd.

General Principles of Treatment

The major principle is that chronic pain conditions almost always represent an interaction among some level(s) of physical pathology (current or previous), pain beliefs, pain responses, genetics, prior or concurrent psychological problems, socioenvironmental factors, and work-site issues. To focus on one of these to the exclusion of others in treating patients is usually inappropriate and inadequate. The management of patients with chronic pain, regardless of what is causing their pain, hinges on supporting those activities and treatments which will improve overall function while remaining realistic about timelines and wide variations in reaching a functional recovery. It is important to explain the relevant anatomy and possible pain sources (or lack thereof) and seek to provide the optimal care for the given condition to manage the pain and minimize dysfunction. Impairing pharmaceuticals and interventional treatments outside of those used for specific conditions with high probabilities of substantial or complete recovery (or short term exacerbations responsive to treatment) should be avoided. Their use should be seriously questioned in those cases when there are no moderate- to high-level RCTs demonstrating efficacy. This is especially true given the extensive body of literature indicating that the placebo effect, expectation bias, and attention bias may be responsible for a significant amount of the benefit that is seen in conjunction with the use of many new interventions or adaptations of interventions used for other conditions, even those that are clearly of benefit when used to manage the medical problem to which they were initially applied.[130-135]

The patient should be transitioned to work or from modified work to full work at the earliest date possible. He or she should be supported during that transition, and told of the likelihood of increased symptoms in conjunction with being reassured that pain does not equate to injury in the chronic pain setting. Should it appear unlikely that there will be anything that can be done to cure the patient's pain, he or she should be informed of that fact, which should be followed with advice that does not equate to disability or hopelessness by stressing that many people have similar conditions yet go to work every day, and take care of their family, leading normal (or nearly normal) lives. The providers' "fear-avoidance beliefs" regarding the relationship between pain complaints and patients' ability to return to work have been shown to affect their treatment practices[136] and, as such, could contribute to a relative nocebo effect. It is consequently imperative that the treating provider be educated regarding exactly what factors are or are not important in developing an appropriate "return-to-work prescription."

Providers should consider referral for further evaluation and perhaps cooperative treatment if:

- Specific clinical findings suggest previously undetected clinical pathology requiring other expertise to adequately address it.
- The clinical course does not follow generally expected patterns:

- Pain distribution is non-anatomic or described in a bizarre or atypical manner. Examples include glove- or stocking-like pain or paresthesias, shock-like pain, pain that radiates up and down the neck and back, burning pain, and pain that is present constantly regardless of position, medication use, or physical treatments.
- Medication use does not decrease as expected, or increases.
- Appropriate active physical therapy does not appear to be improving function as expected.
- Complaints of pain or dysfunction start to involve other body areas, including instances in which the patient:
  - Ceases to discuss returning to work in a specific time frame but rather in relation to a "cure."
  - Fails to benefit from any, or all, rational therapeutic interventions.
  - Experiences increased pain, or at the very least, pain does not decrease, over time.
  - Is unwilling to discuss his or her family situation or expresses comfort with role reversal at home.
  - States that the illness or injury has caused all of his or her problems.
  - Directs excessive anger at the employer or coworkers, the provider, or an insurer and/or demonstrates an attitude of revenge or wanting to prove that he or she is sick.
  - Is less interested in the home therapy program or even in recovery of function.
- There appear to be indications of significant psychosocial dysfunction or psychiatric comorbidity.

Judicious referral may be warranted to corroborate the absence of physical pathology and to assure the patient that increased participation in usual activities will not be detrimental to his or her overall physical status. This must be a referral to a well-qualified provider whose practice patterns are consistent with evidence-based medicine, as the potential to do harm by obtaining an MRI or other diagnostic study labeled "abnormal" based upon the presence of anatomic but clinically irrelevant findings is high. Such labeling may further reduce function and increase disability even if there is nothing abnormal for that person's age group in part by leading to a relative "nocebo effect."

Specific Treatment Interventions

Studies evaluating the efficacy of a variety of treatments in the management of various chronic pain disorders sometimes test interventions, especially medications, in patients with heterogeneous chronic pain disorders. The evidence base for these interventions is discussed in general terms, with individualized indications for use in management of a specific pain state provided when warranted. Treatment of specific disorders is discussed in other guidelines and that specific guidance takes precedent over this guidance.

The emphasis and management of patients with chronic pain is far different than that for acute pain from new physical injuries. For patients with chronic pain rather than acute pain patients, the concentration on pain treatment with medications and invasive interventions is de-emphasized, while the focus should be on functional restoration. The three most important aspects of functional restoration include active patient engagement through interventions that: 1) change the patient's focus

to functional recovery; 2) include aerobic and strengthening exercises; and 3) apply psychological interventions that include enhancing self-modulation of pain and distress. There are some invasive interventions with efficacy in limited circumstances.

Treatments widely used in the management of chronic pain, regardless of etiology, are medications, physical therapy, and occupational therapy (active and judicious use of passive interventions), coordinated multidisciplinary medical and psychological specialty programs, and certain types of injections. The following is the overall discussion of each intervention and information regarding the evidence-basis for recommendations. A summary of the recommendations by chronic pain condition is provided at the beginning of each section.

Chronic Persistent Pain and Chronic Pain Syndrome

Summary of Recommendations

The following summary table contains recommendations for evaluating and managing chronic persistent pain from the Evidence-based Chronic Pain Panel. These recommendations are based on critically appraised higher quality research evidence or, when such evidence was unavailable or inconsistent, on expert consensus as required in ACOEM's Methodology. Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient – Recommended (Consensus-based), "I" Level
- Insufficient – No Recommendation (Consensus-based), "I" Level
- Insufficient – Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

Laboratory Tests for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Antibodies to Confirm Specific Disorders	Recommended, Insufficient Evidence (I)
ANSAR Testing for Diagnosing Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Nonspecific Inflammatory Markers for Screening for Inflammatory Disorders	Recommended, Insufficient Evidence (I)
Cytokine Tests for Diagnosing Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Needle EMG and Nerve Conduction Study to Diagnose	Recommended, Insufficient Evidence (I)
Surface EMG for Diagnosing Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Functional MRIs for Diagnosing Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Local Anesthetic Injections for Diagnosing Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
SPECT/PET for Diagnosing Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
FCEs for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Bed Rest for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Sleep Posture	Recommended, Insufficient Evidence (I)
Specific Beds or Other Commercial Sleep Products	Not Recommended, Insufficient Evidence (I)
Aerobic Exercise for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Strengthening Exercise for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Stretching Exercise for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Aquatic Therapy for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)

Yoga for Other Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Physical or Occupational Therapy for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Oral NSAIDs for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Acetaminophen for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Norepinephrine Reuptake Inhibitor Anti-depressants for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Selective Serotonin Reuptake Inhibitors (SSRIs), Bupropion, or Trazodone for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Duloxetine for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Anti-convulsant Agents (Except Topiramate) for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Topiramate for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Gabapentin and Pregabalin for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Clonidine	No Recommendation, Insufficient Evidence (I)
Epidural Clonidine for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Ketamine Infusion for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Dextromethorphan for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Glucocorticosteroids for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Ketanserin for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Muscle Relaxants for Acute Exacerbations of Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Topical NSAIDs for Chronic Persistent Pain Where Target Tissue Superficially Located	Recommended, Insufficient Evidence (I)
EMLA Cream for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Lidocaine Patches for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Tumor Necrosis Factor-alpha Blockers for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Magnets and Magnetic Stimulation for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Taping and Kinesiotaping for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Self-application of Cryotherapies for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)
Provider-applied Cryotherapies for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Self-application of Heat Therapy for CRPS or Other Chronic Pain Syndromes	Recommended, Insufficient Evidence (I)
Diathermy for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
External Radiation for Sympathetic Blockade for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Ultrasound for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Provider-based or self-application of Infrared Therapy for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Low-level Laser Therapy for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Manipulation for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Massage for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Mechanical Massage Devices for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Myofascial Release for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Acupuncture for Chronic Persistent Pain	Recommended, Insufficient Evidence (I)

Reflexology for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
High-voltage Galvanic Therapy for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
H-Wave® Device Stimulation for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Interferential Therapy for Chronic Persistent Pain.	No Recommendation, Insufficient Evidence (I)
Iontophoresis for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Microcurrent Electrical Stimulation for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
PENS for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
TENS for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Intrapleural Bupivacaine Infusions for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Lidocaine Infusion for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Intrathecal Drug Delivery Systems for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)
Ziconotide for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Psychological Evaluation for Chronic Persistent Pain Patients	Recommended, Insufficient Evidence (I)
Fear Avoidance Belief Training	Recommended, Insufficient Evidence (I)
Biofeedback	Recommended, Insufficient Evidence (I)
Cognitive Behavioral Therapy	Moderately Recommended, Evidence (B)
Herbal and Other Preparations for Chronic Persistent Pain	No Recommendation, Insufficient Evidence (I)
Vitamins for Chronic Persistent Pain	Not Recommended, Insufficient Evidence (I)

Related Terms

- Non-specific pain
- Low Back Pain (see Lumbar Spine Disorders Guideline)
- Neck Pain (see Cervical and Thoracic Spine Disorders Guideline)
- Mid-back Pain (see Cervical and Thoracic Spine Disorders Guideline)
- Thoracic Pain (see Cervical and Thoracic Spine Disorders Guideline)
- Non-specific Hand Pain (see Hand, Wrist, Forearm Disorders Guideline)
- Non-specific Forearm Pain (see Hand, Wrist, Forearm Disorders Guideline)
- Myofascial Pain Syndrome (see Shoulder Disorders Guideline)
- Trigger Points (see Shoulder Disorders Guideline)
- Fibromyalgia (see Fibromyalgia Guideline)
- Tender Points (see Fibromyalgia Guideline)
- Osteoarthrosis
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Polymyalgia rheumatic
- Rheumatological Disease
- Autoimmune disease
- Osteomalacia
- Porphyrias
- Cancers/neoplasias
- Pain Disorder
- Malingering
- Colitis

- Irritable Bowel Syndrome
- Munchausen's
- Somatization Disorder
- Conversion Disorder
- Psychogenic Pain

Overview

Chronic persistent pain signifies pain of at least 3 months duration. Chronic persistent pain is closely related to Chronic Pain Syndrome, which is generally considered to have additional features such as limited functional status, vocational status, and/or significant psychological features. As the precise diagnosis determines the best treatment strategies, this guideline is superseded by all guidelines that address specific conditions. For example, low back pain is the most common cause of chronic persistent pain and chronic pain syndrome. Approximately 10% of the workers have ongoing chronic low back pain, and 25% of workers have sufficient low back pain episodes that they do not achieve a 90-day pain-free interval [137]. Yet, treatment of LBP is specific and there is evidence for and against specific interventions to treat it that are found in the ACOEM Low Back Disorders Guideline.

Psychiatric disorders factor prominently in the differential diagnosis for chronic pain disorders that have been evaluated and have no discrete diagnosis. These psychiatric disorders include somatization disorder, conversion disorder, psychogenic pain disorder, and Munchausen's. Malingering is also a significant potential explanation, especially in worker's compensation settings where secondary gains are considerable.

The purpose of this guideline is to provide guidance for the treatment of chronic pain disorders without a defined diagnosis, whether chronic persistent pain or chronic pain disorder. Guidance for specific diagnoses is provided in diagnostic-specific guidelines. Psychiatric/psychological evaluation and diagnosis is primarily addressed in the Psychiatric/Psychological Pain Evaluation Guideline.

Risk and Causation

A method for determination of work-relatedness is discussed in detail in the Work-Relatedness Guideline. There are naturally no quality epidemiological studies associating chronic, undiagnosed painful condition(s) with occupational tasks. Most worker's compensation jurisdictions will not recognize ongoing treatment of a non-specific and undiagnosed painful condition. This is largely as a conclusion of work-relatedness is thus speculative.

By contrast, systematic literature reviews and syntheses are provided for specific disorders, such as a discussion of work-relatedness of low back pain that is discussed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines and thus also not duplicated here. Complex Regional Pain Syndrome is addressed in that section of the Chronic Pain Guideline. Fibromyalgia is discussed in that section of the Chronic Pain Guideline. Osteoarthroses are discussed in body-part specific guidelines. Myofascial pain syndrome is discussed in Shoulder Disorders Guideline.

Signs and Symptoms

If the patient has been evaluated but remains undiagnosed, most remaining patients typically have:

- Aching, burning pain
- Non-neurological pain distribution
- Pain often, but not always worse with activity; often more noticeable at night, perhaps due to less distraction by other issues
- Weakness sometimes present; may be related to deconditioning or avoidance of pain
- Normal examination or may have abnormalities that include non-specific muscle weakness

Diagnosis

Initial Assessment

The initial assessment is focused on attempting to diagnose a cause for chronic pain. See Introductory section of this guideline. After an initial evaluation is performed, but the chronic pain condition remains undiagnosed, the evaluation should particularly focus on an evaluation to determine the presence of, and extent of, potential psychiatric and psychosocial factors that may be causing or contributing to the chronic pain condition.

Table 5. Diagnostic Criteria for Non-Red Flag Conditions

Probable Diagnosis or Injury	Symptoms	Signs	Tests and Results
Chronic Persistent Pain	Pain for at least 3 months. Pain that is for 12 plus hours out of 24, or pain limiting specific activities (sleep, mood, or appetite disturbances may be present)	None, other than specific for a discrete entity (e.g., osteoarthrosis)	Diagnostic tests if targeting the specific body part and there is a potential for meaningful intervention. See body part-specific guidelines for evaluation and diagnostic testing (e.g., low back pain or shoulder pain).
Chronic Pain Syndrome*	Pain for at least 3 months. Enduring or recurring pain persisting longer than typical for an associated condition Inadequate response to appropriate care Marked restriction in daily activities Excessive medication use and frequent use of medical services Excessive dependence on health providers, spouse and/or family; withdrawal from social milieu, i.e., work or other social contacts	Marked alteration in behavior with frequent depression or anxiety Significant, reliable impairment of functional status inadequately explained by physical findings Evidence of possible psychological dysfunction such as anxiety, fear-avoidance, depression or significant pain or illness behaviors (may have "deconditioning" or poor aerobic endurance)	Same as chronic persistent pain regarding a diagnostic evaluation. Also, psychological evaluation (including diagnostic testing as indicated) may be useful

**Chronic pain is defined as 3 months duration or longer.*

Classification

There is no common classification system for chronic persistent pain or chronic pain syndrome. Most would classify all causes of any type of chronic persistent pain and categorize into discrete, known disorders (e.g., low back pain, osteoarthrosis, etc.). Once discrete diagnostic entities are removed from the population with chronic pain, the remainder could be categorized in terms of degree of impairment or disability (e.g., working full duty, working limited duty, not working).

History

A general approach is provided, as the differential diagnosis for chronic pain is vast (see prominent examples in the Differential Diagnosis section), it is beyond this guideline to provide a complete discussion of such an extensive topic.

The initial queries follow standard lines of questioning for patients with pain (e.g., function, onset, trauma history, location of pain, presence of tingling/numbness, aggravating factors, relieving factors). Initial queries should be sufficient to identify and categorize the chronic persistent pain into a body region affected and to begin to rule out various types of causes of chronic pain. Additional questions should seek to identify causal or contributing factors. These initial queries have the primary purposes of beginning to identify: 1) body part(s) affected, 2) probable diagnosis, 3) level of function and 4) causal factors.

Care should be taken to identify potential causal factors and address both occupational and non-occupational components to optimize the clinical outcome. A detailed occupational history to identify potentially causative factors is highly recommended.

As psychosocial factors and psychiatric disorders figure prominently in chronic pain syndromes, early queries to identify these factors are also important.

Physical Exam

Physical examination maneuvers should include a comprehensive neuromusculoskeletal exam to identify all positive and negative aspects in an attempt to secure a correct diagnosis. These maneuvers include observation, inspection, palpation, cranial nerve examination, range of motion, strength, stretch reflexes, coordination, balance, and sensory exam.

Diagnostic Recommendations

Laboratory Tests for Chronic Persistent Pain

Recommended.

Laboratory tests are recommended as a screen to evaluate specific disorders (e.g., diabetes mellitus, alcohol) that may cause or contribute to chronic persistent pain

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Indications:	Patients with symptoms suggestive of peripheral neuropathies without prior diagnostic evaluations. Diagnostic testing should generally include fasting glucose and either hemoglobin A1c and/or 2-hour glucose tolerance testing. The threshold for testing for signs of alcohol should also be quite low (i.e., CBC with Mean Cell Volume, GGTP, AST and ALT). Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor.
Benefits:	Diagnosing a latent condition. As there is evidence that multiple disorders interact to raise risk of neuropathy, addressing all causes is also thought to produce a more favorable prognosis.
Harms:	Negligible
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated when either there is a significant change in exposure (e.g., substantial weight gain) or symptoms change.
Rationale:	Diagnosis or diabetes mellitus (or glucose intolerance) and alcohol abuse is important to treat to prevent peripheral neuropathy and progression[138-148]. Serological tests are minimally invasive, unlikely to have substantial adverse effects, are low to moderately costly depending on the specific test ordered, have evidence of diagnostic efficacy and are thus recommended for focused testing of a few diagnostic considerations.
Evidence:	There are no quality studies evaluating laboratory testing for the diagnosis of chronic persistent pain syndrome.

Antibodies to Confirm Specific Disorders

Recommended.

Antibodies are recommended as a screen to confirm specific disorders (e.g., rheumatoid arthritis, lupus) and for assessing patients with chronic persistent pain

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Indications:	Undiagnosed patients with either systemic arthropathies and/or peripheral neuropathies, or patients have had incomplete evaluations. Diagnostic testing should generally include sedimentation rate. Other tests may include rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin in presence of peripheral neuropathy) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.

Benefits:	Diagnosing an unknown condition. Providing opportunity to prevent destruction of joints.
Harms:	Negligible
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated when either there is a significant change in symptoms. A second evaluation is also indicated if the first evaluation is negative; thus, typical symptoms persist and there is a rationale to expect increased titers on a delayed basis compared with the initial assessment. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.
Rationale:	Elevated antibody levels are highly useful for confirming clinical impressions of rheumatic diseases. However, routine use of these tests may result in inaccurate diagnoses due to false positives especially if there is a low pre-test probability. Measurement of antibody levels is minimally invasive, unlikely to have substantial adverse effects, and is low to moderately costly depending on the specific test ordered. They are recommended for focused testing of a few diagnostic considerations. However, ordering of a large, diverse array of antibody levels without diagnostically targeting a few specific disorders is not recommended.
Evidence:	There are no quality studies evaluating antibodies for the diagnosis of chronic persistent pain syndrome.

ANSAR Testing for Diagnosing Chronic Persistent Pain

Not Recommended.

ANSAR testing is not recommended to assist in diagnosing chronic persistent pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale:	ANSAR has not been shown to alter the clinical management of patients with chronic persistent pain. The value of identifying abnormalities in autonomic tone, if they exist, has not been demonstrated. The value of pharmacologically treating such abnormalities if they are clinically silent and manifested by positive test results has also not been identified. ANSAR is non-invasive, has minimal risk of adverse effects depending on the maneuvers performed, but is moderately costly. ANSAR is not recommended for evaluation of patients with chronic persistent pain.
Evidence:	There are no quality studies evaluating ANSAR for the diagnosis of patients with chronic persistent pain.

Non-specific Inflammatory Markers for Screening for Inflammatory Disorders

Recommended.

Erythrocyte sedimentation rate, CRP and other inflammatory markers are recommended for screening for signs of systemic inflammation among those with chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Undiagnosed patients with symptoms consistent with either systemic rheumatological diseases and/or peripheral neuropathies, or patients have had incomplete evaluations. Subsequent, additional tests may be needed, including rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.
Benefits:	Diagnosing an unknown condition. Opportunity to prevent joint destruction.
Harms:	Negligible
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated when either there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.
Rationale:	Erythrocyte sedimentation rate is the most commonly used systemic marker for non-specific, systemic inflammation and is elevated in numerous inflammatory conditions as well as with infectious diseases. C-reactive protein has been linked with an increased risk of coronary artery disease. However, it is also a non-specific marker for other inflammation. Other non-specific markers of inflammation include ferritin, and an elevated protein-albumin gap, however those two markers appear to have no known clinical roles. CRP and ESR measurements are minimally invasive, have low risk of adverse effects and are low cost. They are recommended as a reasonable screen for systemic inflammatory conditions especially in patients with chronic persistent pain without clear definition of a diagnosis and/or with incomplete explanation of symptoms. However, test results should be interpreted cautiously as the specificity is not high. The ordering of a large, diverse array of anti-inflammatory markers without targeting a few specific disorders diagnostically is not recommended, as it the utility of such wide batteries of tests is dubious.
Evidence:	There are no quality studies evaluating non-specific inflammatory markers for the diagnosis of chronic persistent pain syndrome.

Cytokine Tests for Diagnosing Chronic Persistent Pain

Not Recommended.

Routine testing with or the use of batteries of cytokine tests is not recommended to diagnose chronic persistent pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:

Cytokines purportedly determine whether a patient is experiencing pain or has suffered a toxicological insult. However, there are no quality studies that address this premise. Available studies suggest that these markers may be elevated in chronic pain conditions, but these studies did not have adequate control groups and did not control for potential confounders. The range of disorders in which cytokines may be elevated also needs definition, as the current range of conditions appears large,[149-157] suggesting they are not specifically isolated to patients with chronic pain, and thus the specificity of these tests seems likely to be quite low.

A high-quality, 7-year study of 880 elderly subjects evaluated impacts of IL-6 and CRP on both cross-sectional associations with morbidity and long-term mortality.[149] CRP and IL-6 were higher among smokers at baseline and those with higher body mass indexes (BMIs). IL-6 and CRP were also higher among those with hypertension, myocardial infarction, stroke, glycosylated hemoglobin levels, HDL, and number of chronic conditions. Both IL-6 and CRP were inversely related to quartiles of moderate and strenuous physical activity. CRP and/or IL-6 were associated with incidence of hypertension, myocardial infarction, diabetes, and incident cases of chronic conditions. Physical performance measures of changes in grip strength, signature time, chair-rise and 6-m fast walk all were not significant for IL-6 or CRP. Cytokines need to be rigorously studied to ascertain if there is a place for them in the evaluation and/or management of chronic pain conditions, including stratification for occupationally-relevant diseases. Documentation that the discovery of elevated cytokine levels results in changes in evaluation and/or clinical management would also be necessary. Alternatively, this testing may be useful if the absence of elevated cytokine levels would warrant concluding that a patient does not have a remediable physical cause of pain. While cytokine testing is minimally invasive, and has a low risk of adverse effects, these tests are high cost, with no evidence that they alter the clinical management of patients with chronic persistent pain. Their place in the evaluation of patients with chronic persistent pain is yet to be determined and cytokine testing is not recommended.

Evidence:

There is 1 high-quality study incorporated into this analysis.

Evidence for the Use of Cytokines

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Taaffe 2005 (score = 8.0)	Cytokines	Prospective Cohort Study	No mention of Sponsorship or COI.	N = 880 age 70-79 participants in MacArthur Study of Successful Aging	Mean Age: 74.3 ± 2.7 years Sex (M:F) 412:458	Plasma IL-6, CRP levels determined by enzyme-linked immunosorbent assay and log transformed to normalize distributions. Physical function measures: handgrip strength, signature time, chair stands, 6-m walk time.	7 years	Women had lower ($p < 0.05$) IL-6 levels. Hours per year undertaking moderate and strenuous physical activity also related to inflammatory markers with higher ($p < 0.001$) IL-6 and CRP levels in less active individuals.	"Although IL-6 has been shown to predict onset of disability in older persons and both IL-6 and CRP are associated with mortality risk, these markers of inflammation have limited associations with physical performance, except for walking measures and grip strength at baseline, and do not predict change in performance 7 years later in a high-functioning subset of older adults."	According to the authors, baseline IL-6 and CRP not associated with change in performance.

Needle EMG and Nerve Conduction Study to Diagnose

Recommended.

Needle EMG and nerve conduction study is recommended for evaluation of select chronic persistent pain patients.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Indications:	Indications include the evaluation of symptoms that are either in one limb or are widespread. Includes the evaluation of potential radicular pain. Also includes the post-surgical population to evaluate the potential for a nerve conduction delay identifiable by NCS with inching/segmental technique. Generally not performed until there is failure to resolve after waiting 4 to 6 weeks to provide for sufficient time to develop EMG abnormalities (usually a minimum of 3 weeks to begin to show significant changes).
Benefits:	Diagnosing an unknown condition. Identification of a neurological conduction delay caused by a scar that is remediable.
Harms:	Negligible. Modest pain from the procedure
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated when either there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.
Rationale:	EMG/NCS is often helpful for helping define the location and extent of neurological impairments. EMG/NCS is minimally invasive, has minimal adverse effects, is moderately costly, has been found to be diagnostically helpful and is thus recommended for diagnosis in select chronic persistent pain patients.
Evidence:	There are no quality studies evaluating EMG/NCS for the diagnosis of chronic persistent pain syndrome.

Surface EMG for Diagnosing Chronic Persistent Pain

Not Recommended.

Surface EMG is not recommended for the differential diagnosis of chronic pain. There are selective indications for use with biofeedback.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale:	Surface EMG has no demonstrated value in the clinical evaluation or treatment of chronic persistent pain with resultant altered management or improved clinical outcomes. Surface EMG may be of use in biofeedback training, and gait analysis for musculoskeletal and/or neurologic disorders, but it has no established use in the management of chronic persistent pain and is thus not recommended.
Evidence:	There are moderate-quality studies evaluating sEMG for the diagnosis of patients with chronic persistent pain.

Evidence for the Use of Surface EMG

Study Type Author/Year	Score	N	Area of Body	Surface EMG (Type)	Needle EMG used for				More than one muscle		Long term follow-up		Results	Conclusion	Comments
Sihvonen 1991 Diagnostic Sponsored by the Yrjo Jahnsson Foundation, no COI.	6.0	112 (51 males, 61 females) Mean age 34.4	L	Averaged electric activity (RMS, EMG)	+	-	-	+	-	-	+	No	There was only a partial decrease of EMG activity after flexion in back pain patients with current pain…The ratio of mean reached at maximal activity level during extension and flexion was less in patients (1.8, SD = 0.5, p <0.001) than able-bodied controls (3.2, SD = 0.8).	"We believe that it (EMG) is an invaluable aid in detecting and objectifying disturbed function in paraspinal muscles in back pain patients and in general disability."	Surface EMG readings from right side of lumbar spine only. Data suggest ratio of EMG activity during extension and flexion to be more sensitive in detecting abnormalities than flexion relaxation phenomenon. Data suggest that absence of flexion relaxation in the lumbar paraspinal muscles correlate well with current LBP.
Ramprasad 2010 Cross sectional Study	4.5	50 (33 males, 17 females)	Rectus Abdominis, Lumbar Erector Spinae	Neurocare TM-advanced 2000 Surface EMG	-	-	-	-	+	+	-	No	Results showed significantly different mean PPR (preprogrammed reactions) and voluntary response RMS amplitudes in LBP group vs. controls for rectus abdominus and erector spinae muscles (p <0.05). Kappa agreement ranged from 0.7 to 1.	"LBP group exhibited poor modulation of highly flexible preprogrammed reactions during perturbation tasks compared to asymptomatic population. A disproportional increase in EMG	Data suggest potential deconditioning in LBP group. Low back patients were older than controls. Data suggest a difference in muscle activation in patients with low back pain compared to controls.

Sponsored by a grant from SCPTRC, Mangalore, Karnataka, India. No mention of COI.		Mean age 36.4											amplitudes of voluntary responses of global trunk muscles to perturbation was associated with poor PPR modulation in the CLBP group compared to asymptomatic participants."	
Ahern 1988 Comparative case-control	3.5	80	L	Surface EMG	-	-	-	-	-	-	+	No	Patients showed average of 27° lumbar flexion compared to 52° in controls. Analysis of FI found 57.5% showed no flexion/relaxation response, vs. 7.5% in controls. (p >0.05). Statistically significant differences between patients and controls for trunk rotation (p <0.01).	"Although the two groups did not differ on absolute levels of EMG during quiet standing, significant differences were found for EMG patterns during dynamic postures. In addition, most patients did not show the flexion-relaxation response or the expected pattern of EMG responses during trunk rotation, most likely because of restricted range of motion and/or compensatory posturing."	Baseline differences in weight (p <0.03). Lack of baseline characteristics including if controls ever had LBP. Data suggest different muscle activity and inactivity patterns in chronic LBP patients vs. controls. Electrodes placed L3-4, L4-5. Data suggest patients with CLBP move/activate muscles differently when moving vs. controls. This can help in developing rehab programs.

Functional MRIs for Diagnosing Chronic Persistent Pain

Not Recommended.

Functional MRIs are not recommended for diagnosing chronic persistent pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	Although there are research studies, there are no quality studies indicating that the findings on fMRIs are of sufficient sensitivity and specificity to permit identification of the presence or absence of chronic persistent pain or to distinguish between different types of chronic pain states. The clinical applications of the test have not been defined. Functional MRI is minimally invasive and has low adverse effects, is high cost, but has no quality evidence of efficacy and is thus not recommended.
Evidence:	There are no quality studies evaluating fMRI for the diagnosis of patients with chronic persistent pain.

Local Anesthetic Injections for Diagnosing Chronic Persistent Pain

Recommended.

Local anesthetic injections are recommended for diagnosing chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Chronic persistent pain in a specific nerve distribution (e.g., ilioinguinal, genitofemoral) that is otherwise unexplained by other investigation, including imaging, EMG/NCS. See TBI Guideline for guidance regarding occipital nerve blocks.
Benefits:	Potential to identify a potentially treatable lesion
Harms:	Medicalization, nerve trauma, and continuing a search for a fixable lesion if one is not to be found.
Frequency/Dose/Duration:	Once.
Rationale:	Local injections (e.g., ilioinguinal, genitofemoral nerve blocks) have not been evaluated in sizable, quality studies for diagnostic, prognostic, or treatment purposes, though they may assist with diagnosis and consideration of potential treatment options and are thus recommended. However, corticosteroid or neuroablative injections/procedures for localized pain for these nerve blocks are not

recommended as the risk of increased pain, local tissue reaction, and neuroma outweigh documented benefits (see Table 6).

Evidence: There are no quality studies evaluating local anesthetic injections for the diagnosis of patients with chronic persistent pain.

Table 6. Adverse Effects of Injections

General complications of neuraxial injections, and of injections near the paravertebral muscles	Infection at site and remote (meningitis found in one German study following trigger point, facet, and epidural injections). Bleeding, including hematoma causing nerve compromise. Direct trauma to nerve, causing permanent damage or increased pain. Injection into the wrong space (artery, vein, inadvertent intrathecal, or thoracic cavity). This can lead to respiratory compromise, cardiac arrest, or pneumothorax.
Complications specifically related to the substance and amount injected (in addition to possible anaphylaxis)	Local anesthetics – seizures, cardiac collapse. Sympatholytics – hypotension, tachycardia, cardiac dysrhythmias. Corticosteroids* – endocrine dysfunction, diabetes, hypertension, dysphoria, immune compromise, phlebitis, muscle pain, osteoporosis, dependency, rarely nerve damage, etc. Baclofen* – anxiety, blurred vision, ataxia, coma, depression, dizziness, dysarthria, dystonic reaction, hallucinations, headache, respiratory depression, seizures, stroke, etc. Botulinum toxins – weakness, paralysis, respiratory compromise, diplopia, dizziness, injection site reaction.

*These adverse effects are mostly temporary aggravations and dependent on dose and frequency.

SPECT/PET for Diagnosing Chronic Persistent Pain

Not Recommended.

SPECT is not recommended to evaluate patients with chronic persistent pain (aside from use in cases of suspected inflammatory arthropathies not diagnosed by more common tests). The use of PET scanning is also not recommended to evaluate patients with chronic persistent pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: SPECT and PET scanning of the brain may be of use in assessing the status of cerebrovascular perfusion, tumors, and neurodegenerative conditions, but aside from providing information of interest for research, these techniques have not been shown to be useful in influencing the management of patients with chronic persistent pain. SPECT scanning may be useful in detecting inflammatory disease in the spine and other areas that might not be amenable to evaluation by other studies. SPECT and PET scanning are minimally invasive, have negligible adverse effects, are high cost, have no quality evidence of efficacy for diagnosis of chronic persistent pain, and so are not recommended.

Evidence: There are no quality studies evaluating SPECT or PET for the diagnosis of patients with chronic persistent pain.

FCEs for Chronic Persistent Pain

Recommended.

FCEs are recommended for evaluating patients with chronic persistent pain to attempt to objectify worker capability vis-à-vis either specific job or general job requirements

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Need to objectify worker capabilities compared with either job specific or general job requirements. Should generally be performed only after treatment options have been utilized, implemented, and stability has been reached with apparent residual deficits,
Benefits:	Assess functional abilities and may facilitate greater confidence in return to work.
Harms:	Medicalization, worsening of pain with testing. May have misleading results that understate capabilities. Because FCEs do not typically address significant cognitive issues (other than following directions and retaining instructions), mismatches in cognitive requirements may go unaddressed.
Frequency/Dose/Duration:	Generally only once unless there is significant passage of time or apparent change in function.
Rationale:	FCEs are one of the few means to attempt to objectify limitations and are frequently used in the workers' compensation system. Because their reliability and validity have not been proven and there are issues with suboptimal efforts that are not necessarily captured, they should be considered as one set of data about what a patient was willing to do on a given day. They should not be used to override the judgment about the work ability of a patient. They particularly should not be viewed as providing objective evidence when there is other corroborating evidence of subjective-objective mismatches or evidence the patient is able to accomplish more than was demonstrated at the time of the FCE. Most patients will not require an FCE, particularly where the patient is able to articulate a desire to return to work, along with stated capabilities that appear to match the clinical impression. An FCE may be helpful in identifying capabilities at an end of healing for purposes of attempting to support work limitations that are used to assign "permanent" restrictions and disability applications. However, providers should be particularly aware of major secondary gain issues when FCEs are performed for these purposes and be particularly vigilant about test-retest reliability, test validity measures, and the need to unequivocally report all measures as well as any evidence of subjective-objective mismatches.
Evidence:	There are no quality studies of the reliability and validity of FCEs for evaluating patients with chronic persistent pain.

Bed Rest for Chronic Persistent Pain

Not Recommended.

Bed rest is not recommended for chronic persistent pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Rationale:	There is no evidence that bed rest is helpful for these conditions and it has been found to be unhelpful for LBP and other conditions. There are potential adverse effects that reportedly have included pulmonary emboli (see Low Back Disorders guideline). Bed rest, although not invasive, has potential for major adverse effects, is costly, has no documented benefits, and thus it is not recommended.
Evidence:	There are no quality studies evaluating bed rest for the treatment of chronic persistent pain syndrome.

Sleep Posture

Recommended.

Altering sleep posture is recommended (if a patient habitually chooses a particular sleep posture) to determine if there is reduction in pain or other symptoms.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Pain that interferes with sleep, especially if there is a pattern of exacerbating the pain with particular posture(s)
Benefits:	Pain reduction and improved sleep with essentially no adverse effects.
Harms:	None
Rationale:	There are no quality studies of sleep posture changes for treatment of neuropathic pain. Changing posture has no adverse effects, has not cost, may be effective and thus is recommended especially if there is a pattern towards worsening symptoms with particular sleep postures.

Specific Beds or Other Commercial Sleep Products

Not Recommended.

Specific beds or other commercial sleep products are not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	There is no quality evidence that specific commercial products have roles in primary prevention or treatment of neuropathic pain, yet they are mostly moderate to high cost and thus are not recommended.
Evidence:	There are no quality studies evaluating specific commercial products for the treatment of chronic persistent pain syndrome.

Treatment Recommendations

Activity Modification and Exercise

Aerobic Exercise for Chronic Persistent Pain

Recommended.

Aerobic exercise is selectively recommended for treatment of chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – High

Indications:	Moderate to severe chronic persistent pain, especially for those with spine-related pain, myofascial-type pain, fibromyalgia or lower extremity osteoarthrosis (see respective guidelines). Also indicated for those with diabetes mellitus and/or significant de-conditioning. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's *Guidelines for Exercise Testing and Prescription,* 9th ed.,[161] in regards to health screening and risk stratification.
Benefits:	Improved function, improved endurance, improved neuropathy control if diabetes is contributing
Harms:	Negligible. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Intolerance of weight bearing in severe lower extremity osteoarthrosis. Other musculoskeletal disorders possible (e.g., plantar heel pain).
Frequency/Dose/Duration:	Start with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Transition to home exercise program. The most detailed program for low back pain was walking at least 4 times a week at 60% of predicted maximum heart rate (220-age = maximum heart rate) is recommended.[162] Benchmarks were 20 minutes during Week 1, 30 minutes during Week 2, and 45 minutes after that point. Nearly all patients should be encouraged to maintain aerobic exercises on a long-term basis additionally to maintain optimal health.

Indications for Discontinuation:	Non-tolerance, failure to progress, development of another disorder, or reaching a 4 to 6 week timeframe.
Rationale:	There is no quality evidence that aerobic exercise is helpful for treatment of chronic persistent pain. Yet, there are numerous quality studies for treatment of many other conditions that demonstrate efficacy for treatment including spinal pain, radicular pain, fibromyalgia, and knee osteoarthrosis (see other ACOEM Guidelines). As well, patients who have diabetes mellitus that is co-contributing to their chronic persistent pain and others who have significant deconditioning due to chronic persistent pain may benefit. Aerobic exercise is not invasive, has negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, has strong rationale for select indications, and thus is selectively recommended.
Evidence:	There are no quality studies evaluating aerobic exercise for the treatment of chronic persistent pain syndrome.

Strengthening Exercise for Chronic Persistent Pain

Recommended.

Strengthening exercise is selectively recommended for treatment of chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Moderate to severe chronic persistent pain; hip osteoarthrosis or knee osteoarthrosis; diabetes mellitus and/or significant strength deficits. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's *Guidelines for Exercise Testing and Prescription,* 9th ed.,[161] in regards to health screening and risk stratification.
Benefits:	Improved function, improved strength, improved ability to perform strength-demanding job tasks
Harms:	Negligible. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Other musculoskeletal disorders possible (e.g., plantar heel pain).
Frequency/Dose/Duration:	Typically start with 3 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Supervised treatment frequency and duration is dependent on symptom severity and acuity and the presence of comorbid conditions. Transition to including home exercises.
Indications for Discontinuation:	Non-tolerance, failure to progress, development of another disorder (e.g., strain), or reaching a 4 to 6 week timeframe.

Rationale: There is no quality evidence that strengthening exercise is helpful for treatment of chronic persistent pain. However, there are many circumstances where strengthening exercise is indicated including patients with spine pain, hip arthrosis, or knee osteoarthrosis (see other ACOEM Guidelines) and those with significant deconditioning with strength deficits, particularly with mismatches between abilities and job demands. Strengthening exercises are not invasive, have negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, have strong rationale for select indications, and thus are selectively recommended.

Evidence: There are no quality studies evaluating strengthening exercise for the treatment of chronic persistent pain syndrome.

Stretching Exercise for Chronic Persistent Pain

No Recommendation.

There is no recommendation for stretching exercise for treatment of chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality studies that stretching exercise is helpful for treatment of chronic persistent pain. Most patients with chronic pain do not have meaningful reductions in range of motion and emphasis on range of motion is usually to the detriment of advancing more functionally important exercises, such as strengthening and aerobic or conditioning. Active-assisted and aggressive stretching is particularly problematic for some patients as there is greater injury potential. However, there are some selective patients with meaningful reductions in range of motion for whom inclusion of flexibility exercises may be of benefit. There are patients with directional exercise benefits for low back pain. Thus there are selective exceptions. Stretching exercises are not invasive, have negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, do not have quality evidence for efficacy in chronic persistent pain patients and thus there is no recommendation. There may be selective exceptions (see above).

Evidence: There are no quality studies evaluating stretching exercise for the treatment of chronic persistent pain syndrome.

Aquatic Therapy for Chronic Persistent Pain

Recommended.

A trial of aquatic therapy is selectively recommended for patients with chronic persistent pain, who meet the referral criteria for supervised exercise therapy and have co-morbidities (e.g., extreme

obesity, significant degenerative joint disease, etc.) that preclude effective participation in a weight-bearing physical activity.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Moderate to severe chronic persistent pain in the lower extremities or torso; non-weight bearing status or partial weight-bearing; with significant de-conditioning. Those with diabetes mellitus may also benefit.
Benefits:	Improved function, improved endurance, improved neuropathy control if diabetes is contributing
Harms:	Negligible
Frequency/Dose/Duration:	Start with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Program should include up to 4 weeks of aquatic therapy with progression to a land-based, self-directed physical activity or self-directed aquatic therapy program by 6 weeks. For some patients with chronic persistent pain, aquatic exercise may be the preferred method. In these few cases, the program should become self managed and if any membership to a pool is covered, coverage should be continued if it can be documented that the patient is using the facility at least 3 times a week and following the prescribed exercise program.
Indications for Discontinuation:	Non-tolerance, failure to progress, or reaching a 4 to 6 week timeframe.
Rationale:	There is no quality evidence that aquatic exercise is helpful for treatment of chronic persistent pain. However, there are circumstances where aquatic exercise are indicated, including patients who are either non-weight-bearing or limited weight-bearing, have deconditioning due to chronic pain, and/or have diabetes mellitus that is co-contributing to their chronic persistent pain. Aquatic exercise is not invasive, has negligible adverse effects, is moderate cost in aggregate, has rationale for select indications, and thus is selectively recommended.
Evidence:	There are no quality studies evaluating aquatic therapy for the treatment of chronic persistent pain syndrome.

Yoga for Other Chronic Persistent Pain

Recommended.

Yoga is recommended for select highly motivated patients with chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Chronic persistent pain conditions in patients motivated to try and adhere to a program of yoga.
Benefits:	Improved conditioning and flexibility. Improved pain control with negligible adverse effects.
Harms:	Negligible
Frequency/Dose/Duration:	at least 3 times per week for at least 20min.
Indications for Discontinuation:	Non-tolerance, non-compliance.
Rationale:	There is moderate-quality evidence of the effectiveness of yoga for the treatment of chronic LBP,[163-165] although there are many different types of yoga and no study results have been replicated. This review assumes that other chronic pain conditions (e.g., CTS,[166] migraines[167]) respond similarly to yoga. There is no quality evidence that yoga is beneficial for treating CRPS or neuropathic pain. However, yoga is not invasive, has low potential for adverse effects, is low cost, has evidence of efficacy for treatment of some conditions and is thus recommended. Evidence also suggests that patient motivation must be high, and there is much self-selection in the reviewed studies, as compliance and adherence reportedly are not good.
Evidence:	There are 5 high- or moderate-quality RCTs incorporated into this analysis (see Low Back Disorders chapter for these studies). There are no quality studies evaluating yoga for the treatment of CRPS or trigger points/myofascial pain. There are no quality studies evaluating yoga for the treatment of chronic persistent pain syndrome.

Physical or Occupational Therapy for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against the use of physical or occupational therapy to treat chronic persistent pain. (See individual treatments that are often administered by these professionals.)

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	These studies are heterogeneous with numerous simultaneous interventions, thus sound conclusions cannot be drawn from them.[168-185] See individual treatment modalities to ascertain the available evidence on specific treatment interventions. See also behavioral pain recommendations regarding cognitive behavioral therapy.
Evidence:	There are moderate-quality RCTs incorporated into this analysis. Also, there are other quality studies on the use of exercises in specific

situations such as ankylosing spondylitic[186] and experimental studies that deal indirectly with potential back pain in healthy study subjects.[187]

Medications

Oral NSAIDs for Chronic Persistent Pain

Recommended.

Oral NSAIDs are recommended for treatment of chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Chronic persistent pain sufficiently severe to require medication. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as first-line medications. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious. Over-the-counter (OTC) agents may suffice and may be tried first. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as first-line medications. Second-line medications should include one of the other generic medications. COX-2 selective agents are recommended as a third- or fourth-line medications when there are contraindications for other NSAIDs and/or there are risks of GI complications; however, concomitant treatment with misoprostol, sucralfate, and proton pump inhibitors are also options for gastro-protection (see Guidelines).
Benefits:	Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. NSAIDs are among the best medications especially for safety sensitive workers.
Harms:	Gastrointestinal adverse effects are especially prominent in those with past history of gastrointestinal bleeding, for which either cytoprotection or Cox-2 agents are advisable. Those elderly, with diabetes mellitus and rheumatological orders also are among those at increased risk. There is some evidence for increased cardiovascular risks, especially in the highly and more-selective NSAID agents. There is no clear evidence of cardiovascular harm from the non-selective NSAIDs ibuprofen and naproxen. (see further discussion in Low Back Disorders). It appears that despite widespread usage, diclofenac does not have clear superiority at least for LBP where it has been trialed, yet may have increased risks for adverse cardiovascular events[188] and is neither recommended nor not recommended for use either alone or in combination with misoprostol (Arthrotec).

Frequency/Dose/Duration:	For most patients, scheduled dosage, rather than as needed, is preferred to avoid adverse effects of other treatment options, but prescribing NSAIDs as needed is reasonable for mild or moderate symptoms. Due to the potential adverse effects from chronic use (more than 2 months) of NSAIDs, patients should be periodically monitored for adverse effects such as hypertension, blood loss, renal insufficiency (as manifested by an increased creatinine), and hepatic enzyme elevations. Older patients and those with co-morbidities may require more frequent monitoring. Use of an adjunctive cytoprotective agent may also be warranted.
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.
Rationale:	There is no quality evidence for treatment of chronic persistent pain, but there is strong evidence of efficacy for treatment of numerous pain conditions, including spine pain, radicular pain, osteoarthrosis, sprains, etc. (see specific ACOEM Guidelines). NSAIDs are not invasive, have low adverse effects in employed populations, are low cost, have evidence of efficacy for treating numerous musculoskeletal disorders and thus inferred for efficacy to treat other chronic persistent pain patients, and are thus recommended.
Evidence:	There are no quality studies evaluating oral NSAIDs for the treatment of chronic persistent pain syndrome.

Acetaminophen for Chronic Persistent Pain

Recommended.

Acetaminophen is recommended for treatment of chronic persistent pain, particularly in patients with contraindications for NSAIDs.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Chronic persistent pain sufficiently severe to require medication. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as first-line medications. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious.
Benefits:	Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. Acetaminophen is among the best medications especially for safety sensitive workers.
Harms:	Negligible if used as prescribed. Renal adverse effects are possible, especially among chronic, high-dose users and those with other renal impairment. Hepatic toxicity in high doses or among those with other

	hepatic impairments (e.g., excessive alcohol consumption). Reduced dosage may be used in such settings, along with close monitoring.
Frequency/Dose/Duration:	Generally prescribed up to 3.5g/day in divided doses, usually QID dosing
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.
Rationale:	There are no quality trials of acetaminophen for treatment of chronic persistent pain. Paracetamol, a close analog, has also not been studied for chronic persistent pain, but does have evidence of efficacy for treatment of LBP, although not as successful as diflunisal,[189] mefenamic acid,[190] indomethacin,[190] or aspirin.[190] There also is evidence of some efficacy for treatment of osteoarthrosis, although it is similarly less effective than NSAIDs (see Knee Disorders Guideline). Thus, while the evidence suggests efficacy of acetaminophen and paracetamol, it appears these medications are modestly less efficacious than NSAIDs (although generally safer) at least for LBP. Acetaminophen is not invasive, has very low adverse effects, is low cost, has evidence of efficacy for treatment of LBP and is thought to have modest efficacy and thus is recommended for treatment of chronic persistent pain.
Evidence:	There are no quality studies evaluating acetaminophen for the treatment of chronic persistent pain syndrome.

Norepinephrine Reuptake Inhibitor Anti-depressants for Chronic Persistent Pain

Recommended.

Norepinephrine reuptake inhibitor anti-depressants (TCAs) are recommended for treatment of chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Chronic persistent pain sufficiently severe to require medication. Generally, NSAIDs and therapeutic exercises are trialed before anti-depressants. Occasionally, anti-depressants are used first especially the sedating properties for nocturnal sleep disturbance due the chronic persistent pain.
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Cardiotoxicity may occur.

Frequency/Dose/Duration:	Prescribe at a low dose at night and gradually increase (e.g., amitriptyline 25mg QHS, increase by 25mg each week) until a sub-maximal or maximal dose is achieved, sufficient effects are achieved, or adverse effects occur. Duration of use for chronic persistent pain patients may be indefinite, although some patients do not require indefinite treatment, particularly if they are compliant with the elements of a functional restoration program.
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.
Rationale:	There is no quality studies suggesting efficacy of tricyclic anti-depressants for treatment of chronic persistent pain. However, there is evidence of efficacy for treatment of some chronic pain conditions, especially spine disorders (see Lumbar Spine Disorders Guideline), thus it is reasonable to suspect other chronic persistent pain conditions may be effectively treated. Norepipnephrine reuptake inhibiting anti-depressants (tricyclic antidepressants) are not invasive, have adverse effects that range from modest to intolerable, are low cost, have indirect evidence suggesting some efficacy for treatment of chronic persistent pain and so are recommended.
Evidence:	There are no quality studies evaluating tricyclic anti-depressants for the treatment of chronic persistent pain syndrome.

Selective Serotonin Reuptake Inhibitors (SSRIs), Bupropion, or Trazodone for Chronic Persistent Pain

Not Recommended.

SSRIs, bupropion, or trazodone are not recommended for chronic persistent pain, other than for fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	There is no quality evidence selective serotonin reuptake inhibitors, bupropion and trazodone are effective for treatment of chronic persistent pain conditions. However, SSRI antidepressants have evidence of efficacy for treatment of fibromyalgia; otherwise, they have no evidence of efficacy for treatment of chronic pain conditions (see Low Back Disorders Guideline). Selective serotonin reuptake inhibitors, bupropion and trazodone are not invasive, have low to modest adverse effects, have no quality evidence of efficacy for treatment of chronic persistent pain and no rationale for believing they may be effective, and so are not recommended for treatment of chronic persistent pain. They may still be indicated for the treatment of depression and/or fibromyalgia.
Evidence:	There are no quality studies evaluating selective serotonin reuptake inhibitors for the treatment of chronic persistent pain syndrome.

Duloxetine for Chronic Persistent Pain

Recommended.

Duloxetine is recommended for limited use in select chronic persistent pain patients as a third-line agent.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Chronic persistent pain that is sufficient to require medication. Generally should also have failed multiple other modalities including trials of NSAIDs, therapeutic exercises, tricyclic anti-depressants, and anti-convulsant agents.
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also has adverse effects including nausea, constipation, dizziness. Serotonin syndrome.
Frequency/Dose/Duration:	There appears to be either a minimal or no advantage of the BID dosing over the 60mg QD dosing. Duration for patients with chronic persistent pain may be as long as indefinitely, although some patients do not require indefinite treatment, particularly if they are compliant with a functional restoration program.
Indications for Discontinuation:	Resolution, development of adverse effects, failure to adhere to a restoration program.
Rationale:	There is no evidence of efficacy of duloxetine for treatment of chronic persistent pain. There is some evidence of efficacy of duloxetine for treatment of other disorders. Duloxetine is not invasive, has low to moderate adverse effects, is moderate cost, has some quality evidence of efficacy for treatment of some chronic persistent pain and is selectively recommended after trials of other treatments.
Evidence:	There are no quality studies evaluating duloxetine for the treatment of chronic persistent pain syndrome.

Anti-convulsant Agents (Except Topiramate) for Chronic Persistent Pain

Recommended.

Carbamazepine is recommended for treatment of chronic persistent pain.

Strength of Evidence **– Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Sufficient chronic persistent pain to require medication. Generally considered a potential adjunct as a fourth- or fifth-line treatment for chronic persistent pain, after attempting other treatments (e.g., different NSAIDs, aerobic exercise, other exercise, tricyclic antidepressants). Oxcarbazepine and lamotrigine may be useful agents to trial if the results from carbamazepine are insufficient.
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also has adverse effects including nausea, vomiting, dizziness. Fluid and electrolyte abnormalities.
Frequency/Dose/Duration:	Frequency and dosing are based on the medication prescribed. Duration of use for chronic persistent pain patients may be indefinite, although many of these patients do not require indefinite treatment as the condition usually often resolves or improves.
Indications for Discontinuation:	Resolution of pain, lack of efficacy, or development of adverse effects. Monitoring of employed patients is indicated due to elevated risks for CNS-sedating adverse effects.
Rationale:	There is high and moderate quality evidence of efficacy of anti-convulsants (Lamotrigine) for treatment of neuropathic pain in comparison with placebo [191][192][193][194]. Although not all studies are positive [195][196], the highest quality studies suggest efficacy. Anti-convulsants are not invasive, have low to moderate adverse effects, are low to moderate cost, have some quality evidence of efficacy for treatment of neuropathic pain and so are selectively recommended after trials of other treatments.
Evidence:	There are no quality studies evaluating anti-convulsants agents (except topiramate) for the treatment of chronic persistent pain syndrome.

Topiramate for Chronic Persistent Pain

Recommended.

Topiramate is selectively recommended for treatment of chronic persistent pain with depression or anxiety.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Chronic spine pain patients with depression or anxiety. Failure of multiple other modalities including trials of different NSAIDs, aerobic exercise, specific stretching exercise, strengthening exercise, anti-

	depressants, and distractants. Not indicated for chronic pain with neuropathic features (see Neuropathic Pain).
Benefits:	Modest reductions in pain and may improve psychological profile. Potential to spare need for more impairing medications.
Harms:	Sedative effects are the highest risks especially in safety-sensitive or cognitively demanding positions. May cause renal stones and ocular toxicity.
Frequency/Dose/Duration:	Topiramate is initiated by gradually increasing the dose – beginning at 50mg and increasing by 50mg/day each week.[197] The most appropriate steady dose is unclear, but appears to be 300mg. Patients should be carefully monitored for the development of adverse events.
Indications for Discontinuation:	Resolution, development of adverse effects, or failure to adhere to a functional restoration program. Careful monitoring of employed patients is indicated due in part to elevated risks for central nervous system- (CNS) sedating adverse effects.
Rationale:	There is no quality evidence of efficacy for treatment of chronic persistent pain. However, there is quality evidence that topiramate is effective for the treatment of chronic LBP[197] (see Low Back Disorders guideline). By contrast, there is quality evidence that topiramate is not effective for treating painful diabetic neuropathy,[195] although a small quality study showed weak benefits.[198] Dropout rates are high with topiramate (37 to 62%), which suggests that the medication is not well tolerated. Topiramate is not invasive, has adverse effects, has quality evidence suggesting a lack of efficacy and thus is not indicated for treatment of chronic persistent pain.
Evidence:	There are high- and moderate-quality RCTs incorporated into this analysis. There are no quality studies evaluating topiramate for the treatment of chronic persistent pain syndrome.

Gabapentin and Pregabalin for Chronic Persistent Pain

Recommended.

Gabapentin and pregabalin are selectively recommended for treatment of chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Moderate to severe painful pain with neuropathic features that has not responded to other treatments, e.g., NSAIDs, therapeutic exercises, tricyclic anti-depressants, and anti-convulsants. May be trialed in chronic persistent pain.
Benefits:	Improved pain control, may include reduced sleep disturbance.

Harms:	Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also has adverse effects including nausea, vomiting, dizziness.
Frequency/Dose/Duration:	Initiate medication at a low dose and gradually increase. Duration of use for patients with chronic persistent pain may be as long as indefinitely, although many of these patients do not require indefinite treatment as the conditions usually either resolve or improve.
Indications for Discontinuation:	Resolution or intolerance. Careful monitoring of employed patients is indicated due in part to elevated risks for CNS-sedating adverse effects.
Rationale:	Gabapentin and its closely related compound pregabalin have been evaluated in quality studies for treatment of multiple pain syndromes. However, the results are not uniformly positive for all conditions. Data are not supportive for lumbar pain. For diabetic peripheral neuropathy, there is evidence that gabapentin[199] and pregabalin[200, 201] are both effective at reducing symptoms. For postherpetic neuralgia, the one available study suggests benefit.[202] There are no other studies identified that attempted treatment of typical nociceptive pain conditions. The remaining study analyzed neurogenic claudication and found significant improvements in distances walked[203] (see also guideline on Low Back Disorders). However, studies do not clearly indicate whether the overall risk/benefit analysis favors use of gabapentin for spine conditions (other than perhaps pre-operatively) given that its use can be associated with moderately significant adverse effects, such as nausea (19%) and dizziness (24%).[199, 203, 204] Gabapentin and pregabalin are not invasive, but have significant adverse effects in some patients, largely central nervous system-related which is of concern in employed populations. Release of a generic form of gabapentin has reduced its cost, although pregabalin remains moderately costly. As there is evidence of efficacy, gabapentin and pregabalin are selectively recommended after trialing multiple other treatments.
Evidence:	There are high- and moderate-quality RCTs or crossover trials incorporated into this analysis. There are no quality studies evaluating gabapentin and pregabalin for the treatment of chronic persistent pain syndrome.

Clonidine

No Recommendation.

There is no recommendation for or against use of clonidine for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	There are no quality studies of clonidine for treatment of chronic persistent pain, although there are some studies of parenteral use. Clonidine is not invasive, has adverse effects, is low to moderate cost cumulatively and in the absence of evidence of efficacy, there is no recommendation.
Evidence:	There are no quality studies evaluating clonidine for the treatment of chronic persistent pain syndrome.

Epidural Clonidine for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against the use of epidural clonidine for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	Quality studies have evaluated intravenous or epidural clonidine both for treating[205] as well as preventing recurrence of pain in a peri-operative timeframe.[206] Both uses have shown benefits. However, there are no quality studies of clonidine for treatment of chronic persistent pain. Epidural clonidine is invasive, has adverse effects, is low to moderate to high cost and in the absence of evidence of efficacy, there is no recommendation.
Evidence:	There is 1 moderate-quality RCT and 1 moderate-quality crossover trial incorporated into this analysis. There are no quality studies evaluating epidural clonidine for the treatment of chronic persistent pain syndrome.

Ketamine Infusion for Chronic Persistent Pain

Not Recommended.

Ketamine infusion is not recommended for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale:	There is no quality evidence of efficacy of ketamine infusions for chronic persistent pain. There are some short-term studies regarding neuropathic pain, but nothing with efficacy over days to weeks. Therefore, ketamine is not recommended for diagnostic or therapeutic use until additional studies demonstrating its clinical efficacy have been reported.

Evidence: There are high-quality RCTs/crossover trials incorporated into this analysis.There are no quality studies evaluating ketamine infusions for the treatment of chronic persistent pain syndrome.

Dextromethorphan for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against dextromethorphan for treatment of patients with chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality studies evaluating NMDA receptor/antagonists for chronic persistent pain. There is limited evidence regarding dextromethorphan for treatment of neuropathic pain.[207-209] Detromethorphan is not invasive, has high adverse effects, has limited evidence of efficacy but only in some patient populations with chronic neuropathic pain and thus there is no recommendation for or against its use in chronic persistent pain.

Evidence: There are high- and moderate-quality RCTs or crossover trials incorporated into this analysis. There are no quality studies evaluating NMDA receptor/antagonists for the treatment of chronic persistent pain syndrome.

Glucocorticosteroids for Chronic Persistent Pain

Not Recommended.

Glucocorticosteroids are not recommended for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale: Glucocorticosteroids to treat radicular pain syndromes and LBP have been assessed in quality studies. Evidence is consistent that steroids are ineffective for treatment of LBP, and minimally effective for very short-term oral use to treat radicular pain.

Systemic glucocorticosteroids are either minimally invasive or not invasive depending on the route of administration. Adverse effects, including avascular necrosis and adrenal suppression, particularly from long-term administration, are significant and the benefits must be carefully weighed against these risks. Diabetic patients may have worsened glucose control while using glucocorticoids. It is low cost to give steroids orally, but may be moderate cost for parenteral routes. There is no evidence for efficacy aside from radicular pain (see Low

Back Disorders Guideline) and thus glucocorticosteroids are not recommended for management of other chronic persistent pain.

Evidence: There are 2 moderate-quality RCTs incorporated into this analysis. There are no quality studies evaluating glucocorticosteroids for the treatment of chronic persistent pain syndrome.

Ketanserin for Chronic Persistent Pain

Not Recommended.

Ketanserin is not recommended for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality studies evaluating ketanserin for the treatment of chronic persistent pain, thus it is not recommended. There is 1 low-quality RCT in Appendix 4.[210]

Evidence: There are no quality studies evaluating ketanserin for the treatment of chronic persistent pain syndrome.

Muscle Relaxants for Acute Exacerbations of Chronic Persistent Pain

Recommended.

Muscle relaxants are selectively recommended for brief use as a second- or third-line agent in acute exacerbations of chronic persistent pain with muscle spasms.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications: Moderate to severe chronic persistent pain with musculoskeletal manifestations, especially muscle spasm. (See Low Back Disorders Guideline for other detailed indications). Not indicated for ongoing chronic pain treatment.

Benefits: Improvement in muscle spasm and pain related to muscle spasm

Harms: Sedation, intolerance, medicalization

Frequency/Dose/Duration: Due to abuse potential, carisoprodol is not recommended. Chlorzoazone and chlormezanone are also not indicated due to incidence of adverse effects. Otherwise initial dose in evening (not during workdays or if patient operates a motor vehicle, though daytime use acceptable if minimal CNS-sedating effects). If significant daytime somnolence results, particularly if it interferes with performance of conditioning exercises and other components of the rehabilitation process or treatment plan, discontinue or prescribe a

reduced dose. Duration for exacerbations of chronic pain is limited to a couple weeks. Longer term treatment is generally not indicated.

Indications for Discontinuation: Resolution of pain, non-tolerance, significant sedating effects that carry over into the daytime, other adverse effects.

Rationale: There are no quality studies evaluating muscle relaxants for treatment of chronic persistent pain. However, they have been evaluated in quality studies evaluating chronic back and neck pain,[211-213] although there are far more studies on acute LBP (see Low Back Disorders guideline).[214] The quality of the studies comparing these agents to placebo are likely overstated due to the unblinding that would be inherent in taking a drug with substantial CNS-sedating effects. The adverse effect profile is concerning.[215] Most concerning is the significant potential for CNS sedation, which has typically ranged between 25 to 50%. There are some studies indicating more than 50% of the patients are affected by CNS sedation. Thus, prescriptions for skeletal muscle relaxants for daytime use should be carefully weighed against the patient's need to drive vehicles, operate machinery, or otherwise engage in occupations where mistakes in judgment may have serious consequences. Skeletal muscle relaxants also have a modest, but significant potential for abuse[216] and their use in those with a history of any substance abuse or dependence should be with caution. They are low cost if generic medications are prescribed. Skeletal muscle relaxants are not recommended for continuous management of subacute or chronic spine pain or other chronic musculoskeletal disorders, although they may be reasonable options for select acute pain exacerbations or for a limited trial as a third- or fourth-line agent in more severely affected patients in whom NSAIDs and exercise have failed to control symptoms.

Diazepam appears to be inferior to other skeletal muscle relaxants,[212, 217] has a higher incidence rate of adverse effects, and is addictive. **Therefore, diazepam is not recommended for use as a skeletal muscle relaxant.** Evidence suggests that carisoprodol is comparable to cyclobenzaprine. Chlorzoxazone has been associated with hepatocellular toxicity. Chlormezanone has been implicated in Stevens-Johnson syndrome and toxic epidermal necrolysis. Carisoprodol is particularly prone to abuse and thus, carisoprodol, chlorzoxazone and chlormezanone are **not recommended.**

Muscle relaxants are not invasive, have significant adverse effects, are low to moderately costly and do not have evidence of efficacy to treat chronic persistent pain. However, they have indications for short term treatment of muscle spasms and exacerbations and are selectively recommended.

Evidence: There are high- and moderate-quality RCTs incorporated into this analysis. There are 2 low-quality RCTs,[218, 219] in Appendix 4. There are no quality studies evaluating muscle relaxants for acute exacerbations for the treatment of chronic persistent pain syndrome.

Topical NSAIDs for Chronic Persistent Pain Where Target Tissue Superficially Located

Recommended.

Topical NSAIDs are selectively recommended for treatment of chronic persistent pain where target tissue is superficially located.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Chronic persistent pain in a superficial area that is amenable to a topical agent. Should generally have intolerance of, or another indication against oral NSAID use.
Benefits:	Improvement in pain and function. Avoidance of gastrointestinal adverse effects of some NSAIDs.
Harms:	Irritation, allergy, having to use on skin that may interfere with some job performance needs
Frequency/Dose/Duration:	Per manufacturer's recommendations
Indications for Discontinuation	Resolution, intolerance, adverse effects, or lack of benefits.
Rationale:	There are no quality studies of treating chronic persistent pain with topical NSAIDs. The target tissue for most, but not all chronic persistent pain with an occupational basis is generally too deep for justification of use of topical NSAIDs. Topical NSAIDs are not invasive, have low adverse effects, are high cost for a typical treatment regimen, and are selectively recommended for treatment of conditions amenable to topical treatment who generally also have intolerance or other contraindication for oral NSAID use.
Evidence:	There are high- and moderate-quality RCTs incorporated into this analysis. There are no quality studies evaluating topical NSAIDs for treatment of chronic persistent pain syndrome

EMLA Cream for Chronic Persistent Pain

Not Recommended.

EMLA cream is not recommended for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	EMLA cream has been used for treatment, although there are no quality studies supporting its efficacy and in the absence of efficacy, it is not recommended for treatment of chronic persistent pain, most of which is too deep to likely be treated by a topical agent.

Evidence:	There is 1 high-quality RCT incorporated into this analysis. There are no quality studies evaluating EMLA cream for the treatment of chronic persistent pain syndrome. There is 1 low-quality RCT[220] in Appendix 4.

Lidocaine Patches for Chronic Persistent Pain

Recommended.

Lidocaine patches are selectively recommended for treatment of chronic persistent pain when there is localized pain amenable to topical treatment.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Moderate to severe chronic persistent pain. Should be superficial location amenable to topical treatment. Should generally have failed NSAID, therapeutic exercise, tricyclic antidepressants, anti-convulsants and topical NSAID.
Benefits:	Modest improvements in pain
Harms:	Dermal irritation and intolerance; may have adverse systemic effects if widespread applications of numerous patches
Frequency/Dose/Duration:	Usually 3 patches per day. Duration of use for chronic, localized pain may be as long as indefinitely, although most patients do not require indefinite treatment. Caution is warranted regarding widespread use of topical anesthetics for potential systemic effects from widespread administration.[221]
Indications for Discontinuation:	Resolution, intolerance, adverse effects, lack of benefits, or failure to progress over a trial of at least 2 weeks.
Rationale:	There are no quality studies for treatment of chronic persistent pain. Topical lidocaine has been suggested to improve pain associated with CTS and appears to be somewhat more effective than naproxen.[222] This provides a limited basis for a consensus recommendation for treatment of chronic persistent pain. Lidocaine patches are not invasive, generally have a low adverse effect profile, are moderate to high cost cumulatively, have some evidence of efficacy for treatment of carpal tunnel syndrome and thus are selectively recommended for treatment of chronic persistent pain.
Evidence:	There is 1 high-quality crossover trial incorporated into this analysis. There are no quality studies evaluating lidocaine patches for the treatment of chronic persistent pain syndrome.

Tumor Necrosis Factor-alpha Blockers for Chronic Persistent Pain

No Recommendation.

There is no recommendation regarding TNF-alpha blockers for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	TNF-alpha blockers have not been evaluated in quality studies.[223, 224] TNF-alpha blockers are minimally invasive, have adverse effects, are high cost and in the absence of efficacy there is no recommendation.
Evidence:	There is 1 high-quality RCT incorporated into this analysis. There are no quality studies evaluating TNF-alpha blockers for the treatment of chronic persistent pain syndrome.

Allied Health Interventions

Magnets and Magnetic Stimulation for Chronic Persistent Pain

Not Recommended.

Magnets and magnetic stimulation are not recommended for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – High

Rationale:	There is no significant evidence base from which to draw conclusions on the utility of magnets as a treatment modality for chronic persistent pain, although quality studies of other musculoskeletal disorders have not shown any indication for use of magnets for treatment. Magnets are not invasive, have no adverse effects, are low cost, have no quality evidence of efficacy and are thus not recommended.
Evidence:	There are 1 moderate-quality RCT and 1 moderate crossover trial incorporated into this analysis. There are no quality studies evaluating magnets for the treatment of chronic persistent pain syndrome.

Taping and Kinesiotaping for Chronic Persistent Pain

Not Recommended.

Taping and kinesiotaping are not recommended for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale:	Taping and kinesiotaping have not been shown effective in quality studies for the treatment of chronic persistent pain. Taping and kinesiotaping are not invasive, have some adverse effects, are moderate cost to high cost depending on length of treatment, have no evidence of efficacy and thus are not recommended for chronic persistent pain.
Evidence:	There are no quality studies evaluating taping and kinesiotaping for the treatment of chronic pain conditions.

Self-application of Cryotherapies for Chronic Persistent Pain

Recommended.

Self-application of cryotherapies are recommended for treatment of chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Moderate to severe chronic persistent pain with sufficient symptoms that an NSAID/acetaminophen and progressive graded activity are believed to be insufficient.
Benefits:	Potential modest reduction in pain. Self-efficacy, although relying on a passive modality.
Harms:	Cold injuries. Time may be devoted to passive modality instead of active exercises.
Frequency/Dose/Duration:	As needed, often 15-20 minutes 3-5 times/day
Indications for Discontinuation:	Non-tolerance, including exacerbation of pain.
Rationale:	Self-application of cryotherapies have not been shown effective in quality studies for the treatment of chronic persistent pain. Cryotherapies are not invasive, have minimal adverse effects, are low cost when self-applied, have no quality evidence of efficacy, but may be a reasonable self-treatment option and thus are selectively recommended.
Evidence:	There are no quality studies evaluating self-application of cryotherapies for the treatment of chronic persistent pain syndrome.

Provider-applied Cryotherapies for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against self-application of cryotherapies for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	Self-application of cryotherapies have not been shown effective in quality studies for the treatment of chronic persistent pain. Cryotherapies are not invasive, have minimal adverse effects, are low to moderate cost depending on the type and length of treatment, have no evidence of efficacy and thus there is no recommendation.
Evidence:	There are no quality studies evaluating provider-applied cryotherapies for the treatment of chronic persistent pain syndrome.

Self-application of Heat Therapy for CRPS or Other Chronic Pain Syndromes

Recommended.

Self-application of low-tech heat therapy is recommended for treatment of chronic persistent pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Applications may be periodic or continuous. Applications should be home-based as there is no evidence for efficacy of provider-based heat treatments. Primary emphasis should generally be on functional restoration program elements, rather than on passive treatments in patients with chronic pain.
Benefits:	Improvement in pain with negligible adverse effects
Harms:	Generally negligible. May detract from active exercises.
Frequency/Dose/Duration:	Self-applications may be periodic. Education regarding home heat application should be part of the treatment plan if heat has been effective for reducing pain.
Indications for Discontinuation:	Intolerance, increased pain, development of a burn, other adverse event.
Rationale:	While there are no quality studies, self-applications of heat are not invasive, have few adverse effects, are low cost, and are thus recommended.
Evidence:	There are no quality studies evaluating the self-application of heat therapy for the treatment of chronic persistent pain syndrome.

Diathermy for Chronic Persistent Pain

Not Recommended.

There is no recommendation for or against diathermy for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	Diathermy has not been shown effective in quality studies for the treatment of chronic persistent pain. Diathermy is not invasive, has minimal adverse effects, is moderate cost depending on length of treatment, has no evidence of efficacy and thus there is no recommendation regarding chronic persistent pain.
Evidence:	There are moderate-quality RCTs (one with two reports) incorporated into this analysis which were primarily designed to evaluate the efficacy of manipulative therapies and utilized diathermy as a control.[225-229] There are no quality studies evaluating diathermy for the treatment of chronic persistent pain syndrome.

External Radiation for Sympathetic Blockade for Chronic Persistent Pain

Not Recommended.

External radiation for sympathetic blockade is not recommended for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale:	While external radiation has been used to treat CRPS, available quality studies suggest it is not effective.[230] There is no quality evidence of efficacy for external radiation for treatment of chronic persistent pain. External radiation is not invasive, has adverse effects, moderate to high cost, has no quality evidence of efficacy and thus, is not recommended for treatment of chronic persistent pain.
Evidence:	There is 1 moderate-quality RCT/crossover trial incorporated into this analysis.
Comments:	There are no quality studies evaluating external radiation for the treatment of chronic persistent pain syndrome.

Ultrasound for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against the use of ultrasound for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no large-size quality studies of ultrasound for the treatment of chronic persistent pain. There appears to be some evidence of efficacy for lateral epicondylalgia (see Elbow Disorders Guideline). Ultrasound is not invasive, has few adverse effects, is moderately costly, but in the absence of quality evidence of efficacy, there is no recommendation for or against its use in treating chronic persistent pain.

Evidence: There are 2 moderate-quality RCTs/crossover trial incorporated into this analysis.[231, 232] There are no quality studies evaluating ultrasound for the treatment of chronic persistent pain syndrome.

Provider-Based or Self-Application of Infrared Therapy for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against infrared therapy for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: Infrared therapy has not been shown effective in quality studies for the treatment of chronic persistent pain. Infrared therapy is not invasive, has minimal adverse effects, is moderate cost depending on length of treatment, has no evidence of efficacy and thus there is no recommendation for chronic persistent pain.

Evidence: There are no quality studies evaluating infrared therapy for the treatment of chronic persistent pain syndrome.

Low-level Laser Therapy for Chronic Persistent Pain

Not Recommended.

Low-level laser therapy is not recommended for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: Low level laser therapy has not been shown effective in quality studies for the treatment of chronic persistent pain. Low level laser therapy is not invasive, has minimal adverse effects, is high cost depending on length of treatment, has no evidence of efficacy and thus it is not recommendation for chronic persistent pain.

Evidence: There are 4 high-and moderate-quality[233-236] RCTs incorporated into this analysis (see Low Back Disorders guideline for studies). There is also 1 moderate-quality RCT for myofascial pain incorporated into this analysis.[237] There are no quality studies evaluating LLT for the treatment of chronic persistent pain syndrome.

Manipulation for Chronic Persistent Pain

No Recommendation.

There is no recommendation for treatment of chronic persistent pain. There may be other indications for manipulation (e.g., see Low Back Disorders Guideline including for radicular pain).

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	There is no quality evidence of efficacy of manipulation for treatment of chronic persistent pain. Spine indications are addressed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines. Manipulation is not invasive, has some potential adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy and thus there is no recommendation for or against manipulation for treatment of chronic persistent pain.
Evidence:	There are moderate-quality RCTs incorporated into this analysis.. There are 23 moderate-quality studies (5 with multiple reports) in the Low Back Disorders guideline. There also are 11 systematic reviews, 1 guideline, and 12 low-quality RCTs included in the Appendix of the guideline on Low Back Disorders. There are no quality studies evaluating manipulation for the treatment of chronic persistent pain syndrome.

Massage for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against the use of massage for patients with chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	There is no quality evidence of efficacy of massage for treatment of chronic persistent pain. Spine indications are addressed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines. Massage is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy and thus there is no recommendation for or against massage for treatment of chronic persistent pain.
Evidence:	There are no quality studies evaluating massage for the treatment of chronic persistent pain syndrome.

Mechanical Massage Devices for Chronic Persistent Pain

Not Recommended.

The use of mechanical massage devices applied by rehabilitation service providers or massage therapists to administer massage is not recommended for chronic persistent pain.[238-240]

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	There is no quality evidence of efficacy of massage devices for treatment of chronic persistent pain. Spine indications are addressed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines. There is evidence reviewed that suggests devices are less effective than traditional massage. Massage devices are not invasive, have minimal adverse effects, are moderately costly, have no quality evidence of efficacy, have been suggested to be less effective than traditional massage, and thus are not recommended for treatment of chronic persistent pain.
Evidence:	There are moderate-quality RCTs incorporated into this analysis. There are no quality studies evaluating massage devices for the treatment of chronic persistent pain syndrome. There are 2 low-quality RCTs,[241, 242] in Appendix 4.

Myofascial Release for Chronic Persistent Pain

No Recommendation.

There is no recommendation for myofascial release for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	There is no quality evidence of efficacy of myofascial release for treatment of chronic persistent pain. Myofascial release is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy and thus there is no recommendation for or against myofascial release for treatment of chronic persistent pain.
Evidence:	There are no quality studies evaluating myofascial release for treatment of chronic persistent pain.

Acupuncture for Chronic Persistent Pain

Recommended.

Acupuncture is recommended to treat chronic persistent pain (see other chapters for specific disorders, especially for low back pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Indications:	Chronic persistent pain, especially torso pain. Patients should have had NSAIDs and/or acetaminophen, stretching and aerobic exercise instituted and have insufficient results. Acupuncture may be considered as a treatment for chronic persistent pain as a limited course during which time there are clear objective and functional goals to be achieved. Consideration is for time-limited use in patients with chronic persistent pain without underlying serious pathology as an adjunct to a conditioning program that has both graded aerobic exercise and strengthening exercises. Acupuncture is only recommended to assist in increasing functional activity levels more rapidly and the primary attention should remain on the conditioning program. In those not involved in a conditioning program, or who are non-compliant with graded increases in activity levels, this intervention is not recommended.
Benefits:	Potential to improve pain control and advance functional exercises and conditioning.
Harms:	Negligible in experienced hands. Pneumothoraces have occurred and puncture of other internal organs has occurred.
Frequency/Dose/Duration:	Evidence does not support specific Chinese meridian approaches, as needling the affected area appears sufficient. Patterns used in quality studies ranging from weekly for a month to 20 appointments over 6 months. However, the norm is generally no more than 8 to 12 sessions. An initial trial of 5 to 6 appointments is recommended in combination with a conditioning program of aerobic and strengthening exercises. Future appointments should be tied to improvements in objective measures and would justify an additional 6 sessions, for a total of 12 sessions.
Indications for Discontinuation:	Lack of improvement, lack of compliance with exercises, lack of incremental functional gain at the end of a treatment course, intolerance.
Rationale:	There are multiple quality trials of acupuncture for treatment of many disorders, especially of low back pain (see Low Back Disorders Guideline). There are no quality trials evaluating acupuncture for treatment of non-specific chronic persistent pain. (One small study found no differences between sham and classic Chinese acupuncture.[243] There are quality studies evaluating acupuncture

for the treatment of chronic pain including chronic neck pain, LBP, osteoarthrosis (especially of the knee), lateral epicondylitis, adhesive capsulitis of the shoulder, and headaches.[133, 244] Many different study designs have been used. These include comparisons with shams that insert needles in non-traditional locations, minimal acupuncture with superficial needling, shams that do not insert needles, and comparisons with non-acupuncture treatments. Some studies have combined the acupuncture with electrical currents, and others have applied electrical currents to acupuncture sites. There is no clear benefit of electroacupuncture over needling. There remain some questions about efficacy of acupuncture,[245, 246] with concerns about biases, e.g., attention and expectation bias, in these study designs. Some, but not all studies, suggest persistence of meaningful benefits beyond the duration of treatment.

The majority of studies have demonstrated that there is no benefit of traditional Chinese acupuncture over other types of acupuncture. The evidence to address that question prominently includes all of the highest quality studies.[247-249] One study that evaluated acupuncture in trigger points found benefit from needling over either traditional acupuncture or acupuncture applied to other sites,[250] but that study has not been replicated. There is similarly a suggestion that superficial needling may be as efficacious as deep needling of muscles,[251] but not all studies have found that result.[252] Thus, aside from having identified that there does not appear to be a benefit from traditional acupuncture over other forms of acupuncture, other aspects of needling need further study. Evidence of benefits from acupuncture is strongest for LBP (see chapter on Low Back Disorders). However, there is consistent evidence of benefit for chronic neck pain.[250, 253-255] There are few quality studies evaluating the utility of acupuncture for treatment of tender and trigger points and they tend to have significant design flaws which limit the strength of conclusions. Efficacy of acupuncture for this indication is suggested by the highest quality study.[250]

Acupuncture when performed by experienced professionals is minimally invasive, has minimal adverse effects, and is moderately costly. Despite significant reservations regarding its true mechanism of action, a limited course of acupuncture may be recommended for treatment of certain specific disorders[244, 256-265] (see other chapters including Elbow Disorders, and Cervical and Thoracic Spine Disorders). Acupuncture is minimally invasive, has low adverse effects, is moderately costly, appears to have some evidence of efficacy, and is recommended.

Evidence: There are no quality studies evaluating acupuncture for the treatment of chronic persistent pain.

Reflexology for Chronic Persistent Pain

Not Recommended.

Reflexology is not recommended for treatment of chronic persistent pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale: There are no quality studies of reflexology for treatment of chronic persistent pain. Reflexology has not been shown beneficial for the treatment of chronic LBP in a moderate-quality study.[266] Reflexology is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, there is elsewhere evidence suggesting lack of efficacy, and thus reflexology is not recommended for treatment of chronic persistent pain.

Evidence: There is 1 moderate-quality RCT incorporated into this analysis. There are no quality studies evaluating reflexology for the treatment of chronic persistent pain syndrome.

Herbal and Other Preparations for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against the use of Harpagoside, willow bark (Salix), Camphora molmol, Melaleuca alternifolia, Angelica sinensis, Aloe vera, Thymus officinalis, Menthe piperita, Arnica montana, Curcuma longa, Tanacetum parthenium, and Zingiber officinale[285].

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality trials for treatment of chronic persistent pain with complementary/alternative medications. There is evidence that harpagoside is effective in the treatment of LBP, thus it could be inferred that it may be also effective for other nociceptive pain. There is one trial comparing harpagoside with a low dose of Vioxx (12.5mg).[286-288] As this was a low dose of Vioxx and there was evidence it was inferior at that dose based on Tramadol tablets consumed, it may be reasonable to infer that harpagoside is somewhat less efficacious than NSAIDs. Safety of this agent also needs to be addressed in larger trials over longer durations. Nevertheless, in those who do not tolerate or have contraindications for NSAIDs, or have a strong preference for the use of herbal remedies, harpagoside may be a reasonable medication for treatment of chronic nociceptive pain. Providers should be cautioned that there are no quality long-term safety data.

It is not surprising that salicin is effective in treating LBP,[289, 290] as this is the plant from which salicylates were derived, and would also be expected to be efficacious for treatment of other nociceptive as well as somewhat efficacious for neuropathic pain. There also is evidence that willow bark (salix) inhibits platelet aggregation, though less strongly than aspirin or other salicylates.[291] When compared to a low dose of rofecoxib, there is no difference, which may suggest that willow bark is inferior to NSAIDs for the treatment of LBP although a trial comparing it to higher doses of a NSAID would be needed in order to state this with certainty. A rational basis for the use of this agent is not apparent when it is directly related to salicylates and it may contain other compounds with potential adverse effects. It is also more expensive than most generic NSAIDs. If salicylates are to be used as treatment, generic aspirin is preferable to willow bark or salicin.

Harpagoside and salicin are taken orally. Neither have long-term demonstrated efficacy and safety, the adverse effects appear low, and they are not costly. Both appear likely to be substantially inferior to prescription dose NSAIDs. Regardless of trials to assess efficacy, over-the-counter agents do not have controls on dose and content, thus there is no recommendation. There also is no quality evidence to support the use of other herbal remedies including Camphora molmol, Melaleuca alternifolia, Angelica sinensis, Aloe vera, Thymus officinalis, Menthe piperita, Arnica montana, Curcuma longa, Tanacetum parthenium, and Zingiber officinale.[285]

Evidence: There are high- and moderate-quality RCTs incorporated into this analysis. There are no quality studies evaluating complementary/alternative medications for the treatment of chronic persistent pain syndrome.

Vitamins for Chronic Persistent Pain

Not Recommended.

Vitamins are not recommended for treatment of chronic pain if there are no documented deficiencies or other nutritional deficit states.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There is no quality evidence of efficacy for the use of vitamins to treat chronic pain disorders. There are indications for use with documented nutritional deficiencies. There are three quality studies with conflicting evidence on the prevention of CRPS among those with fractures treated with vitamin C.[292] Whether this finding is applicable to working-age adults is unclear.

Vitamins are not invasive, have low adverse effects (aside from high dose fat soluble vitamins), are low to moderate cost cumulatively, but

in the absence of quality evidence of efficacy, they are not recommended.

Evidence: There are high- and moderate-quality RCTs incorporated into this analysis. There are no quality studies evaluating vitamins for the treatment of chronic persistent pain syndrome.

Electrical Therapies

High-voltage Galvanic Therapy for Chronic Persistent Pain

Not Recommended.

High-voltage galvanic therapy is not recommended for treatment of chronic persistent pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality studies of high-voltage galvanic for treatment of chronic persistent pain. High-voltage galvanic is not proven efficacious for the treatment of chronic LBP or other chronic pain conditions. The single quality study suggests possible minimal, brief improvement for neck pain.[267] High-voltage galvanic is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, there is elsewhere evidence suggesting lack of efficacy, and thus high-voltage galvanic is not recommended for treatment of chronic persistent pain.

Evidence: There is 1 moderate-quality RCT evaluating high-voltage galvanic stimulation for chronic neck pain, but no quality studies evaluating high-voltage galvanic for treatment of chronic persistent pain.

H-Wave® Device Stimulation for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against H-Wave® Device Stimulation for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	There are no quality studies of H-Wave® Device Stimulation for treatment of chronic persistent pain. H-Wave® Device Stimulation is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus there is no recommendation for or against H-Wave® Device Stimulation for treatment of chronic persistent pain.
Evidence:	There are no quality studies evaluating H-Wave® Device Stimulation for treatment of chronic LBP, chronic persistent pain, CRPS, trigger points/myofascial pain, or other chronic pain conditions.

Interferential Therapy for Chronic Persistent Pain.

No Recommendation.

There is no recommendation for or against interferential therapy for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale:	There are no quality studies of interferential therapy for treatment of chronic persistent pain. Interferential is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus there is no recommendation for or against interferential for treatment of chronic persistent pain.
Evidence:	There are no quality studies evaluating interferential therapy for the treatment of chronic persistent pain syndrome.

Iontophoresis for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against iontophoresis for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality studies of iontophoresis for treatment of chronic persistent pain. Iontophoresis is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus there is no recommendation for or against iontophoresis for treatment of chronic persistent pain. There may be limited indications for very superficial pain amenable to topical treatment (see Elbow Disorders and Hand, Wrist and Forearm Disorders Guidelines).

Evidence: There are no quality studies evaluating iontophoresis for treatment of chronic persistent pain (see Elbow Disorders guideline for studies on iontophoresis for lateral epicondylalgia).

Microcurrent Electrical Stimulation for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against microcurrent electrical simulation for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality studies of microcurrent for treatment of chronic persistent pain. Microcurrent is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus there is no recommendation for or against microcurrent for treatment of chronic persistent pain.

Evidence: There are no quality studies evaluating microcurrent electrical stimulation for treatment of chronic LBP, CRPS, trigger points/myofascial pain, or other chronic pain conditions.

PENS for Chronic Persistent Pain

No Recommendation.

PENS is neither recommended nor not recommended outside of research settings for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality studies of PENS for treatment of chronic persistent pain. There are studies in mostly non-radicular back pain patients (see Low Back Disorders Guideline). PENS is minimally invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus there is no

recommendation for or against PENS for treatment of chronic persistent pain.

Evidence: There are 6 moderate-quality RCTs incorporated into this analysis (see Low Back Disorders guideline for these studies). There is also 1 guideline and 2 low-quality RCTs in the Appendix of the guideline on Low Back Disorders. There are no quality studies evaluating PENS for treatment of CRPS, trigger points/myofascial pain or chronic persistent pain syndrome .

TENS for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against TENS for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are quality studies of TENS for several outcomes,[268-270] but no trial has demonstrated large effects and there are no sizable quality studies of chronic persistent pain. TENS is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus there is no recommendation for or against TENS for treatment of chronic persistent pain.

Evidence: There are high- and moderate-quality RCTs or crossover trials incorporated into this analysis. There are 2 low-quality RCTs[271, 272] in Appendix 4. See Low Back Disorders guideline for additional studies. There are no quality studies evaluating TENS for the treatment of chronic persistent pain syndrome

Injection Therapies

Intrapleural Bupivacaine Infusions for Chronic Persistent Pain

Not Recommended.

Intrapleural bupivacaine infusions are not recommended for treatment of chronic persistent pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Rationale: Intrapleural bupivacaine infusions have not been evaluated in sizable quality studies for diagnostic, prognostic, or treatment purposes regarding chronic persistent pain. These infusions are invasive, have potential adverse effects, are costly, have no evidence of efficacy and thus are not recommended for treatment of chronic persistent pain patients.

Evidence: There are no quality studies evaluating intrapleural bupivacaine for treatment of patients with chronic persistent pain.

Lidocaine Infusion for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against the use of lidocaine infusions for treatment of chronic persistent pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality studies of chronic persistent pain. However, there are 7 high- or moderate-quality studies evaluating the short-term safety and effectiveness of this treatment. Disorders studied principally included diabetic neuropathy,[273-276] CRPS,[277] spinal cord injury,[278] and post-operative pain.[279] The longest duration of follow-up with reported data appears to be 14 days,[275, 276] with most studies reporting results for less than 1 day. Most study results have been positive,[274-277] but some have been negative.[278, 279] Overall response rates among chronic persistent pain patients reported are approximately 10 to 50%.[276, 278, 279] No intermediate or long-term quality studies on treatment efficacy have been reported. There is one pilot study that suggests a duration of improvement of 4 hours[277] and a few suggesting improvements for up to 14 days.[276, 277] There are no quality studies that show relief up to or beyond 1 month. The available data suggest duration of pain relief is proportionate to the dose administered.[276, 277] One cohort of 99 chronic persistent pain patients reported 42% of patients had at least a 30% reduction in pain.[280] The same author recommended restriction of this procedure to those patients who could not take oral medications.[281] There is no evidence that these infusions result in a sustained decrease in pain medication requirements, reported pain, or an increase in overall function. Lidocaine infusions are invasive, have significant, dose-related adverse effects,[276, 277, 279] and are moderate to high cost depending on the number of treatments. While an adverse event would not be expected to be common, it could be serious or catastrophic. Thus, the intensity of monitoring required is unclear. Duration of treatment success is neither demonstrated nor predicted to be intermediate to long term. Repeated infusions without objective evidence of prolonged efficacy and functional improvement are not recommended. There are no large, quality studies evaluating the safety and effectiveness of this treatment. Lidocaine infusions are invasive, have adverse effects, are high cost, have not been evaluated in sizable, quality studies for diagnostic, prognostic, or treatment purposes and thus there is no recommendation.

Evidence: There are high- and moderate-quality RCTs or crossover trials incorporated into this analysis. There are 2 low-quality RCTs,[282, 283]

in Appendix 4. There are no quality studies evaluating lidocaine infusion for the treatment of chronic persistent pain syndrome.

Intrathecal Drug Delivery Systems for Chronic Persistent Pain

Not Recommended.

Intrathecal drug delivery systems are not recommended for treatment of chronic persistent pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: Intrathecal drug delivery systems have not been evaluated in quality studies for treatment of non-specific chronic persistent pain. Intrathecal drug delivery systems may be potentially beneficial in limited situations (e.g., those involving malignant pain conditions and terminal patients) but these situations are beyond the scope of this guideline.) Intrathecal opioid delivery systems are invasive, have significant adverse effects including fatalities, potential long-term sequelae from both implantation/retention of the devices, including granuloma formation, and those associated with the concurrent use of intrathecal opioids.[284] These systems could potentially be indicated in those who have failed multiple trials of different oral medications and other treatments and have undergone independent psychological consultation including psychometric testing that does not reveal a contraindication to implantation. Patients considered for implanted opioid delivery systems should be evaluated regarding their suitability for protracted use of systemic opioids. They should have documented compliance with all chronic oral opioids treatment criteria, previously shown to be responsive to oral opioids with documented improved function (but unmanageable adverse effects that use of these systems would be able to overcome).

Evidence: There are high-quality RCTs incorporated into this analysis. There are no quality studies evaluating intrathecal drug delivery systems for the treatment of chronic persistent pain syndrome.

Ziconotide for Chronic Persistent Pain

No Recommendation.

There is no recommendation for or against intrathecal ziconotide for treatment of chronic persistent pain. See Opioids guideline for use of opioids with intrathecal drug delivery systems.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There is one trial of only 6 days for treatment of chronic non-malignant pain with intrathecal administration after failure of opioids that suggested short term benefits. However, there are no trials of

	sufficient duration to provide evidence-based recommendations for treatment in chronic pain patients.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex sympathetic dystrophy; ziconotide; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 41 articles in PubMed, 0 in Scopus, 0 in CINAHL, 652 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria. There are no quality studies evaluating ziconotide for the treatment of chronic persistent pain syndrome.

Behavioral and Psychological Interventions

Psychological Evaluation for Chronic Persistent Pain Patients

Recommended.

A psychological evaluation is recommended as part of the evaluation and management of patients with chronic persistent pain in order to assess whether psychological factors will need to be considered and treated as part of the overall treatment plan.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – Moderate

Indications:	Moderate to severe chronic persistent pain patients, especially those with chronic pain syndrome who also have ongoing debility, mismatches between subjective and objective findings, evidence suggestive of psychological disorder(s), adjustment difficulties, coping problems, and/or substances use issues.
Benefits:	Identify psychological factors and begin treating those to remove those barriers to rehabilitation
Harms:	Negligible
Frequency/Dose/Duration:	One evaluation. Ongoing treatment as indicated by the results of the initial evaluation
Indications for Discontinuation:	Largely negative results from an evaluation, resolution, and/or treatment to a level of acceptable stability.

Rationale:	There are no quality trials of psychological evaluations. Such assessments are routinely accomplished for the various purposes given above, including treatments for which various levels of evidence are provided herein, e.g., functional rehabilitation or interdisciplinary pain programs, candidacy for certain procedures, or chronic use of opioid medications. Evaluations are not invasive, have negligible adverse effects, are moderate cost, have clinical evidence of efficacy and are thus selectively recommended.
Evidence:	There are no quality studies evaluating psychological evaluation for treatment of chronic nonmalignant pain or chronic pain syndromes.

Prognosis

The prognosis for chronic persistent pain is largely determined by the cause and the ability to treat or remove the underlying cause, or causes if multiple.

Differential Diagnosis

The differential diagnosis of chronic persistent pain is extensive. Below are some of the more common causes, rather than a complete list.

- Non-specific pain
- Low back pain (see Low Back Disorders Guideline)
- Neck pain (see Cervical and Thoracic Spine Disorders Guideline)
- Mid-back pain (see Cervical and Thoracic Spine Disorders Guideline)
- Thoracic pain (see Cervical and Thoracic Spine Disorders Guideline)
- Non-specific hand pain (see Hand, Wrist, Forearm Disorders Guideline)
- Non-specific forearm pain (see Hand, Wrist, Forearm Disorders Guideline)
- Myofascial pain syndrome (see Shoulder Disorders Guideline)
- Trigger points (see Shoulder Disorders Guideline)
- Fibromyalgia (see Fibromyalgia Guideline)
- Tender points (see Fibromyalgia Guideline)
- Osteoarthrosis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyalgia rheumatic
- Rheumatological disease
- Autoimmune disease
- Osteomalacia
- Porphyrias
- Cancers/neoplasias
- Pain disorder
- Malingering
- Colitis
- Irritable bowel syndrome
- Munchausen's
- Somatization disorder
- Conversion disorder

- Psychogenic pain

Complications / Comorbidities

- Psychiatric morbidities
- Job dissatisfaction
- Familial stressors
- Co-worker disagreements
- Disagreements with supervisors
- Diabetes mellitus
- Alcohol
- Autoimmune disorders
- Nutritional deficiencies
- Pernicious anemia
- Herpes zoster/shingles

Follow-up Care

It is **Recommended (I)** that patients with work-related chronic persistent pain should have a follow-up visit every 1 to 2 weeks initially by a new health care provider or while still out of work. Appointments should generally be time-contingent, i.e., scheduled as opposed to obtained secondary to changes in pain complaint. The initial appointments should focus on identifying a specific diagnosis and any remediable causes of chronic persistent pain.

Initial visits should include an ongoing focus on function, obtaining more information from the patient, confirming that the history information is consistent, observing for injury/illness behaviors, confirming the diagnosis, and assessing the need for psychological referral and evaluation. The educational process of informing the patient about functional status and the need to engage in a functional rehabilitation program focusing on restorative exercises should be reinforced. These restorative exercise program components should be labeled the cornerstone of the medical management plan for the patient's pain. Other means of managing pain, including pharmaceuticals, should be addressed. Initial visits for chronic pain should also include information to avoid bed rest, excessive rest, or appliances. The provider should take care to answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery.

Subsequent follow-up is **Recommended (I)** to be less frequent and tailored to the patient's needs. In cases where the patient is at work, fully functional, and on minimal or steady-state maintenance NSAID medications, follow-up every 6 to 12 months is **Recommended (I)**. However, in the active rehabilitation phase for patients with chronic persistent pain, follow-ups weekly for as much as 2 or 3 months are **Recommended (I)** to also be conducted if there is need for physical therapy and occupational therapy to sustain a team-oriented focus on restoration and achievement of functional goals.

Job Analysis

The primary purpose of job analyses for patients with chronic persistent pain, especially after failure to secure a diagnosis, is to identify potential exposures that may suggest more probable work-related diagnoses. Other purposes include to identify job demands and the work environment so that accommodations might be identified to help the worker stay at, or return to work. It also provides

treating clinicians with useful information for treatment-work activities to be addressed in treatment. This usually begins with a patient history, then supervisor interview, and subsequently observing the job and potentially obtaining measurement of job physical exposures. If there is concern for neurotoxins and neuropathic pain, see discussion in Neuropathic Pain.

Complex Regional Pain Syndrome

Summary of Recommendations

The following summary table contains recommendations for evaluating and managing complex regional pain syndrome from the Evidence-based Chronic Pain Panel. These recommendations are based on critically appraised higher quality research evidence or, when such evidence was unavailable or inconsistent, on expert consensus as required in ACOEM's Methodology. Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient – Recommended (Consensus-based), "I" Level
- Insufficient – No Recommendation (Consensus-based), "I" Level
- Insufficient – Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

Antibodies for Diagnosing Chronic Pain with Suspicion of Rheumatological Disorder	Recommended, Insufficient Evidence (I)
Antibodies to Confirm Specific Rheumatological Disorders	Strongly Recommended, Evidence (A)
ANSAR Testing for Diagnosing CRPS	Not Recommended, Insufficient Evidence (I)
Bone Scanning for Diagnosing CRPS	Recommended, Evidence (C)
Non-specific Inflammatory Markers for Screening for Inflammatory Disorders	Recommended, Evidence (C)
Cytokine Tests for Diagnosing CRPS and Chronic Pain	Not Recommended, Insufficient Evidence (I)
Surface EMG for Diagnosing CRPS and Chronic Pain	Not Recommended, Insufficient Evidence (I)
Functional MRIs for Diagnosing CRPS	Not Recommended, Insufficient Evidence (I)
Local Anesthetic Injections for Diagnosing CRPS	Recommended, Insufficient Evidence (I)
QSART for Diagnosing CRPS	No Recommendation, Insufficient Evidence (I)
SPECT/PET for Diagnosing Chronic Pain	Not Recommended, Insufficient Evidence (I)
Thermography for Diagnosing CRPS	No Recommendation, Insufficient Evidence (I)

Bed Rest for CRPS	Not Recommended, Insufficient Evidence (I)
Aerobic Exercise	Recommended, Insufficient Evidence (I)
Strengthening Exercises	Recommended, Insufficient Evidence (I)
Stretching Exercises	No Recommendation, Insufficient Evidence (I)
Mirror Therapy for CRPS	Recommended, Evidence (C)
Aquatic Therapy for CRPS	Recommended, Insufficient Evidence (I)
Desensitization Techniques for CRPS	Recommended, Insufficient Evidence (I)
Yoga for CRPS	No Recommendation, Insufficient Evidence (I)
Oral NSAIDs for CRPS	Recommended, Insufficient Evidence (I)
Acetaminophen for CRPS	Recommended, Insufficient Evidence (I)
Intravenous NSAIDs for CRPS	Recommended, Evidence (C)
Norepinephrine Reuptake Inhibitor Anti-depressants for CRPS4	Recommended, Insufficient Evidence (I)
Duloxetine for CRPS	Recommended, Insufficient Evidence (I)
Selective Serotonin Reuptake Inhibitors (SSRIs), Bupropion, or Trazodone for CRPS	Not Recommended, Insufficient Evidence (I)
Anti-convulsant Agents for CRPS	No Recommendation, Insufficient Evidence (I)
Short-term Use of Gabapentin or Pregabalin for CRPS	Recommended, Evidence (C)
Bisphosphonates for CRPS	Strongly Recommended, Evidence (A)
Calcitonin for CRPS	Recommended, Evidence (C)
Clonidine for CRPS	Recommended, Evidence (C)
Intravenous Regional Anesthesia with Clonidine for Preventive Administration Prior to Surgery	Recommended, Evidence (C)
Oral Glucocorticosteroids for CRPS	Recommended, Evidence (C)
Intrathecal Glucocorticosteroids for CRPS	Not Recommended, Evidence (C)
Ketamine Infusion for CRPS	Not Recommended, Insufficient Evidence (I)
Ketanserin for CRPS	No Recommendation, Insufficient Evidence (I)
Magnesium Sulfate for CRPS	Not Recommended, Evidence (C)
NMDA Receptor/Antagonists	Not Recommended, Insufficient Evidence (I)

Muscle Relaxants for CRPS	No Recommendation, Insufficient Evidence (I)
Thalidomide and Lenalidomide for CRPS	Not Recommended, Evidence (C)
Capsicum Creams for CRPS	No Recommendation, Insufficient Evidence (I)
DMSO for CRPS	Recommended, Insufficient Evidence (I)
N-Acetylcysteine (NAC) for CRPS	Recommended, Insufficient Evidence (I)
EMLA Cream for CRPS4	No Recommendation, Insufficient Evidence (I)
Tumor Necrosis Factor-alpha Blockers for CRPS	Not Recommended, Insufficient Evidence (I)
Intravenous Immunoglobulin (IVIG) for CRPS	Recommended, Evidence (C)
Vitamin C for Prevention of CRPS in Patients with Fractures, Extreme Trauma, or High Risk for CRPS	No Recommendation, Insufficient Evidence (I)
Mannitol for Treatment of CRPS	Not Recommended, Evidence (C)
Opioids	See guideline
Hyperbaric Oxygen for CRPS	No Recommendation, Insufficient Evidence (I)
Magnets and Magnetic Stimulation for CRPS	Not Recommended, Insufficient Evidence (I)
Occlusal Splint for CRPS	Not Recommended, Insufficient Evidence (I)
Taping and Kinesiotaping for CRPS	Not Recommended, Insufficient Evidence (I)
Acupuncture for CRPS	No Recommendation, Insufficient Evidence (I)
Cryotherapies for CRPS	Not Recommended, Insufficient Evidence (I)
Self-application of Heat Therapy for CRPS	Recommended, Insufficient Evidence (I)
Diathermy for CRPS	Not Recommended, Insufficient Evidence (I)
External Radiation for Sympathetic Blockade for CRPS	Not Recommended, Evidence (C)
Infrared Therapy for CRPS	Not Recommended, Insufficient Evidence (I)
Low-level Laser Therapy for CRPS	No Recommendation, Insufficient Evidence (I)
Manipulation for CRPS	No Recommendation, Insufficient Evidence (I)
Massage for CRPS	No Recommendation, Insufficient Evidence (I)
Myofascial Release for CRPS	Not Recommended, Insufficient Evidence (I)
Reflexology for CRPS	Not Recommended, Insufficient Evidence (I)
High-voltage Galvanic Therapy for CRPS	Not Recommended, Insufficient Evidence (I)

H-Wave® Device Stimulation for CRPS	No Recommendation, Insufficient Evidence (I)
Interferential Therapy for CRPS	Not Recommended, Insufficient Evidence (I)
Iontophoresis for CRPS	Not Recommended, Insufficient Evidence (I)
Microcurrent Electrical Stimulation for CRPS	Not Recommended, Insufficient Evidence (I)
PENS for CRPS	Not Recommended, Insufficient Evidence (I)
Sympathetic Electrotherapy for CRPS	Not Recommended, Insufficient Evidence (I)
TENS for CRPS	No Recommendation, Insufficient Evidence (I)
Botulinum Injections for CRPS	No Recommendation, Insufficient Evidence (I)
Intrathecal Baclofen for CRPS	Recommended, Insufficient Evidence (I)
Intrapleural Bupivacaine Infusions for CRPS	Not Recommended, Insufficient Evidence (I)
Lidocaine Infusion for CRPS	No Recommendation, Insufficient Evidence (I)
Stellate Ganglion Blocks for CRPS	Recommended, Evidence (C)
Guanethidine Bier Blocks for CRPS	Strongly Not Recommended, Evidence (A)
Phentolamine Bier Blocks for CRPS	No Recommendation, Insufficient Evidence (I)
Bretylium Bier Blocks for CRPS	Recommended, Evidence (C)
Methylprednisolone Bier Blocks for CRPS	Not Recommended, Evidence (C)
Reserpine Bier Blocks for CRPS	Not Recommended, Insufficient Evidence (I)
Brachial Plexus Blocks and Infusions for CRPS	No Recommendation, Insufficient Evidence (I)
Spinal Cord Stimulators for Short- to Intermediate-term Relief of CRPS	Recommended, Evidence (C)
Amputation for CRPS	Not Recommended, Insufficient Evidence (I)

Related Terms

Reflex sympathetic dystrophy
Causalgia
Algodystrophy
Nerve pain
Radicular pain
Radiculitis
Diabetic neuropathy
Alcoholic peripheral neuropathy
Central nerve pain

Peripheral nerve pain
Phantom limb pain
Shingles

Overview

Complex regional pain syndrome (CRPS) is a severely painful condition that is most often associated with recent trauma or injury. It has been variously defined by the International Association for the Study of Pain (IASP)[293] and the "Budapest Criteria" as generally including the presence of diffuse moderate to severe non-dermatomal pain, usually with allodynia [294].

CRPS has a reported prevalence of 20.6 to 113.5 per 100,000 adults [295, 296]. It has sometimes been categorized into subtypes, including warm and cold. There are only two population based studies that report incidence of CRPS. The first found an incidence rate of 5.46 per 100,000 person years. Another study reported an annual incidence at 26.2 per 100,000 person years (95% CI 23.0-29.7). Females are diagnosed with CRPS 3.4 times more frequently than males, and incidence is highest among the 50-70 age range. Upper extremity injuries are more commonly associated with CRPS as compared to lower extremities, and a fracture is the most common injury type associated with CRPS. The risk of CRPS has been estimated at 1% among patients with distal radius fractures [297].

Work-Relatedness

A method for determination of work-relatedness is discussed in detail in the Work-Relatedness Guideline. A discussion of work-relatedness of radicular pain is discussed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines and upper extremity disorders in the Hand, Wrist and Forearm Disorders Guidelines and thus aspects that may be relevant for some patients are not duplicated here.

CRPS is reported most frequently after a traumatic insult, [298-301] central nervous system insults including strokes [302], myocardial infarction, or other major system insult[303]. Yet there is controversy regarding work-relatedness for some cases. This is due to: limited insight into the pathophysiology of the syndrome, use of this diagnosis without objective evidence, reported advocagenic influences,[4] and apparent lack of a dose-response relationship between injury severity and probability of the disease. Among patients who have unequivocal evidence of the diagnosis and an overt traumatic occupational injury, work-relatedness of this condition is usually relatively non-controversial as the setting of the trauma determines the causal conclusion and those cases arising from an occupational trauma are usually considered occupational injuries and diseases. CRPS Type II involves an overt nerve lesion,[304] thus the cause of the overt nerve lesion determines the work-relatedness of CRPS Type II. There are relatively infrequent occasions where the cause is unknown (approximately 5 to 15%). In such cases, a determination of work-relatedness is necessarily speculative. As well, when there is either controversy over the diagnosis or an overt, significant occupational injury is not apparent, work-relatedness of CRPS is controversial.

[4] An *advocagenic illness* is a response to legal counsel or legal system, induced or magnified by the counsel or system itself; usually used for unfavorable responses.

Diagnosis

Symptoms and Signs

- Constant severe burning or throbbing pain typically isolated to in one limb
- Trauma often precedes symptoms, and symptoms are disproportionate to the trauma
- Non-radiating pain
- Significantly worsening pain with activity
- Sensitivity to touch, unusual sensitivity and pain to minor pressure or palpation
- Sensitivity to cold
- Skin coloration changes, including blanching and mottling
- Swelling of the affected limb
- Skin texture changes
- Changes in hair and nails

Initial Assessment

The initial assessment requires a thorough history and physical examination with somewhat different emphases compared with most chronic pain patient evaluations. This includes a history of symptoms, trauma, purported cause of the symptoms, treatments attempted, and exercises performed. The history and physical examination require particular attention to differences in use of the limb, strength, color, and temperature. Selective testing may be needed to confirm the clinical impression. The most important emphasis is exclude other potential explanatory conditions.

Diagnostic Criteria

Most of the diagnostic criteria reported include common characteristics for the diagnosis of CRPS [305] [306] [307] [199, 308] however, there have been some differences in case definition criteria [309, 310]. Table 7 has what may be the most used and supportable criteria.

Table 7. Diagnostic Criteria for CRPS for Clinical Purposes*

1. Continuing pain that is disproportionate to the inciting event.
2. At least one symptom in three of these four categories: ▪ *Sensory:* hyperesthesia and/or allodynia ▪ *Vasomotor*: temperature asymmetry and/or skin color changes and/or skin color asymmetry ▪ S*udomotor/edema:* edema and/or sweating changes and/or sweating asymmetry ▪ *Motor/trophic:* decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. At least one sign at evaluation in two or more of the following categories:

▪ *Sensory:* evidence of hyperesthesia to pinprick and/or allodynia to light touch, and/or temperature sensation, and/or deep somatic pressure and/or joint movement ▪ *Vasomotor:* evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry ▪ *Sudomotor/edema:* evidence of edema and/or sweating changes and/or sweating asymmetry ▪ *Motor/trophic:* evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. *Diagnosis:* CRPS is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

*Adapted from IASP 1994[51], Harden et al, *Pain Med*. 2007;8(4):326-31.[311] and Harden et al, *Pain Med.* 2013;14:180-229.

The criteria in Table 7 are recommended for diagnosing CRPS, but may be inadequate as objective measurements and equipment such as temperature probes, volumetry, goniometers and pain scales are required [312]. For patients not meeting the diagnostic criteria, or if CRPS either continues or progresses, the diagnosis of CRPS should be confirmed via a completely independent medical examination (i.e., an exam by someone other than the treating physician). Such an examination should particularly focus on the absence of another explanatory diagnosis, the presence of a temporal inciting event, the historical information particularly from a credible patient, objective evidence (e.g., bone scan), presence of a known nerve injury (CRPS II), and application and comparisons with the diagnostic criteria (copies of which could be sent to the examiner at the time of the independent medical examination). The threshold for concomitant psychological consultation and psychometric testing in such circumstances should be quite low.

An additional major issue is that the diagnosis may previously have been made on purely subjective grounds, without objective evidence[313, 314]. Thus, the original IASP criteria has been modified many times (see Table 7)[128, 311, 315-317]. However, even these significant advancements may be insufficient as the inter-rater reliability scores among physician examiners were reported as adequate, but the numeric data suggest otherwise [312]. Another study also showed evidence that range of motion measurements were not inconsequential [318].

Classification

Complex regional pain syndrome is traditionally classified as either Type I or Type II. Type I is associated with a specific event, such as a fracture or crush injury. Type II is associated with a defined nerve lesion.

History

As CRPS most commonly starts with an injury or event, the medical history naturally starts with the details of that event. Characteristics of pain are then elicited that are unusual and disproportionate compared with the degree of the injury. Excessive sensitivity to normally nonpainful stimuli, such as pressure on the skin develops. Unusual and asymmetric temperature differences between the limbs occur frequently. Cold intolerance is common. Edema occurs. Later changes include skin texture, nails

and hair. Disuse and weakness of the limb becomes nearly universal, especially if the condition is not recognized early and strengthening and conditioning exercises not prescribed.

Physical Examination

The physical examination of a patient with well-established signs of CRPS is almost always straight-forward particularly for the examiner familiar with CRPS. However, early findings are often clinically subtle and the diagnosis may be more tentative. Still the primary intervention is the same: education and directed specialized physical/occupational therapy with primary emphasis on strengthening, functional active use, and aerobic components to prevent dysfunction. Early psychological interventions may benefit selected individuals as well, particularly if there is concomitant post-traumatic stress disorder and/or poor coping (Speck 2016). Often the patient will be observed limiting use of the extremity, including protecting and avoiding use of the limb. This can include not shaking hands or weight bearing on the affected limb.

A key feature of this condition is that objective findings in the affected extremity contrast significantly with those of the unaffected extremity. The skin temperature may differ, usually being cooler in the affected extremity, although it can be warmer. If advanced, the skin may have a smooth, thinned, atrophic appearance [311]. Skin coloration changes are also generally present, including mottling. Livido reticularis (a mottled purplish discoloration of the skin) may be present. The extremity may become edematous. With passage of time, the nails may also become atrophic. A distinguishing characteristic is allodynia, or the experience of pain with something that normal individuals would not consider painful. Examples include pain with light touch, shaking hands, or even the weight of the clothing on the extremity. Circumferences of the affected extremity may differ. They may be increased in edematous states (generally earlier), and reduced if there is disuse dystrophy in chronic states. Water displacement volumes may be measured to attempt to ascertain degrees of swelling, although the baseline measures will not be comparable with the pre-morbid state, which is unknown. Additional findings reported include misperceiving the correct finger that is being touched, inability to identify an object solely with tactile input (astereognosis), and hand laterality identification with motor imagery [319]. While occasional measurements may be acceptable, there is a tendency towards preoccupation with those measures by some, which has the potential to draw attention away from active therapy, towards symptoms and signs, and may inadvertently promote delayed recovery.

Diagnostic Recommendations

Antibodies for Diagnosing Chronic Pain with Suspicion of Rheumatological Disorder

Recommended.

Antibody levels are recommended as a screen to confirm specific disorders (e.g., rheumatoid arthritis, lupus) and for assessing patients with suspicion for rheumatological disorder.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – High

Indications:	Undiagnosed patients with either systemic arthropathies and/or peripheral neuropathies, or patients have had incomplete evaluations. Diagnostic testing should generally include sedimentation rate. Other tests may include rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin in presence of peripheral neuropathy) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.
Benefits:	Diagnosing an unknown condition. Providing opportunity to prevent destruction of joints.
Harms:	Negligible
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated with a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.
Rationale:	Elevated antibody levels are highly useful for confirming clinical impressions of rheumatic diseases. However, routine use of these tests may result in inaccurate diagnoses due to false positives especially if there is a low pre-test probability. Measurement of antibody levels is minimally invasive, unlikely to have substantial adverse effects, and is low to moderately costly depending on the specific test ordered. They are recommended for focused testing of a few diagnostic considerations. However, ordering of a large, diverse array of antibody levels without diagnostically targeting a few specific disorders is not recommended.
Evidence:	Complex regional pain syndrome– A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. There are no quality studies evaluating antibodies for the diagnosis of patients with CRPS.

Antibodies to Confirm Specific Rheumatological Disorders

Strongly Recommended.

Antibodies are strongly recommended as a screen to confirm specific rheumatological disorders (e.g., rheumatoid arthritis) and for assessing patients with possible myofascial pain syndrome, especially with other symptoms.

Strength of Evidence – **Strongly Recommended, Evidence (A)**
Level of Confidence – High

Rationale: Elevated antibody levels are highly useful for confirming clinical impressions of rheumatic diseases. However, routine use of these tests in patients with CRPS is likely to result in inaccurate diagnoses due to false positives and low pre-test probabilities. Measurement of antibody levels is minimally invasive, unlikely to have substantial adverse effects, and is low to moderately costly depending on the specific test ordered. They are recommended for focused testing of a few diagnostic considerations. **However, ordering of a large, diverse array of antibody levels without targeting a few specific disorders diagnostically is not recommended.**

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. There are no quality studies evaluating antibodies for the diagnosis of patients with chronic pain.

ANSAR Testing for Diagnosing CRPS

Not Recommended.

ANSAR testing is not recommended to assist in diagnosing CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: ANSAR has not been shown to alter the clinical management of patients with CRPS. ANSAR is non-invasive, has minimal risk of adverse effects depending on the maneuvers performed, but is moderately costly. ANSAR is not recommended for evaluation of patients with CRPS.

Evidence: There are no quality studies evaluating ANSAR for the diagnosis of patients with chronic pain.

Bone Scanning for Diagnosing CRPS

Recommended.

Bone scanning is selectively recommended to confirm the diagnosis of CRPS of over 6 months duration.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – Low

Indications:	Symptoms of possible CRPS generally for at least 3-6 months, with an uncertain diagnosis.
Benefits:	Identification of significantly asymmetric findings consistent with disuse of a limb.
Harms:	Radiation exposure, minor adverse effects associated with venipuncture.
Frequency/Dose/Duration:	One evaluation. A second would be rarely indicated, e.g., concerns about occult fracture.
Rationale:	There are 15 quality studies evaluating the utility of bone scans for the diagnosis of patients with CRPS. Bone scanning has quality evidence of utility as a good diagnostic test to evaluate suspected metastases, infected bone (osteomyelitis), inflammatory arthropathies, and trauma (e.g., occult fractures). It is believed to be reasonably effective for evaluating patients with moderate to severe CRPS [320][321][322][323], as bone metabolic changes occur over time. The sensitivity and specificity have been estimated in a metanalysis of studies with clearly defined diagnostic criteria at 80% and 73% respectively. While bone scans do not provide direct evidence to support the diagnosis of CRPS, they may reveal osteopenia or osteoporosis, which if unequivocally asymmetric, would presumably be secondary to relative disuse of the body part tested as a result of the disease. In those patients where the diagnosis is felt to be secure, there is not an indication for bone scanning as it does not alter the treatment or management. Bone scanning has modest risks associated with radiation, is high cost, has likely efficacy for limited use and is thus selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. There are moderate quality studies incorporated into this analysis.

Author Year (Score)	Category:	Study type:	Conflict of Interest	Sample size:	Age/Sex:	Diagnoses	Comparison	Results:	Conclusion:	Comments:
Kozin, 1981 (score=6.5)	Scintigraphy	Diagnostic	No mention of sponsorship or COI.	N=64 patients	Mean age: 48.3±15.2 years. 28 males, 36 females.	Reflex sympathetic dystrophy syndrome	Stellate ganglion blockade vs Systemic oral corticosteroid therapy	The grip strength was reduced 136.2±16.8 mmHg in the affected hand compared with contralateral hand. Tenderness scores were greater in affected hand (95.5±8.5 U. Osteopenia was found in 81% of patients with definite RSDS, 45% with probably RSDS, and 57% with possible RSDS. Of the patients where scintigraphs were taken, 44% were positive. Half of patients in groups I-IV showed asymmetrical radionuclide activity. Forty-nine percent of patients had both positive roentgenograms and scintigraphs, whereas 33% were negative. None of 20 patients receiving stellate ganglion blockade had a good response. Sixty-three percent of patients had a good to excellent response to systemic corticosteroid therapy.	"Scintigraphy was found to be a useful diagnostic study that may also provide a method of predicting therapeutic response. Systemic corticosteroid therapy proved to be a highly effective mode of treatment for up to 90% of the patients with RSDS."	Data suggest bone scans are superior (far more specific) to x-ray without loss of sensitivity (86% vs 71%). Also, positive bone scans are helpful in guiding therapy as 90% of patient with positive bone scans responded well to corticosteroid therapy which was determined to be highly effective for treating RSDS.
Schürmann, 2007 (score=6.5)	Scintigraphy	Diagnostic	Sponsored by Friedrich Baur Stiftung München. No mention of COI.	N=148 patients with distal radial fracture	Mean age: 59.9 years; 47 males, 111 females.	Complex Regional Pain Syndrome Type I	Three-phase bone scans vs bilateral thermography vs plain radiographs, and contrast enhance MRI	Combined diagnostic procedures showed an increased sensitivity of 55%, specificity of 87%. Combination of positive results in TPBS or MRI showed low sensitivity of 18% and specificity of 98%.	"Clinical findings remain the gold standard for the diagnosis of CRPS I and the procedures described above may serve as additional tools to establish the diagnosis in doubtful cases."	Data suggest use of imaging studies to screen for CRPS I are unreliable and clinical findings should be considered the gold standard for accurate diagnosis.
Wüppenhorst, 2009 (score=6.5)	Scintigraphy	Diagnostic	Sponsored by BMBF grants (German	N=78 patients	Mean age: 49.94 years; 40 males, 38 females.	Complex Regional Pain Syndrome	3 phases of Bone Scintigraphy	Investigators show sensitivity of 31% and 51% due to high false-negative CRPS diagnoses. Bone scans showed high specificity between 83% and 100%. In all 3 phases of scintigraphy,	"In conclusion, TPBS is a highly specific tool for diagnosing CRPS of the upper limb. ROI evaluative of phase 3	Data suggest TPBS is highly specific for a diagnosis of CRPS in the upper extremity.

			Research Network on Neuropathic pain, DFNS). No mention of COI.					mean ROI scores of CRPS patients were higher than that of control group. Phase 2-3 differed significantly. Sensitivity decreased to 50% for ascending ROI scores whereas specificity increase to 94-100%. Length of CRPS until TPBS was only variable with significant impact on ROI scores of phase 3 (F=23.7; p=0.000; R^2=.42). ROI scores decreased with increasing time of CRPS.	within first 5 months after onset of CRPS is an appropriate additional diagnostic tool to confirm or exclude CRPS of the upper extremity.	
Schweitzer, M 1995 (score=5.5)	Scintigraphy	Diagnostic	No reported COI from all authors. No Mention of sponsorship	51 patients with Reflex Sympathetic Dystrophy (SDR)	22 males, 29 females; mean age 42.	Reflex Sympathetic Dystrophy syndrome.	T1- and t2-weighted sequence vs T1-weighted sequences with fat suppression before and after the intravenous administration of contrast material	RSD confirmed in 45 patients at clinical examination. 35 patients had confirmed RSD by 6 month follow-up. MR images were positive in 39 patients (sensitivity, 87%; specificity, 100%. Positive predictive value of MR imaging was 100%, negative predictive value 45%. At MR imaging, 35 had stage 1, 5 stage 2, 5, stage 3. MR imaging of stage 1 most accurately demonstrated (31 of 35) contrast enhancement (31 of 35 patients), infrequently sof-tissue edema (6 of 35 patients). Stage 2 RSD most difficult to accurately stage. (2 of 5) had skin thinning, (2 of 5) skin thickening; enhancement was unusual and was seen in only (1 of 5). No patients with soft tissue or muscle edema. Stage 3 RSD no enhancement seen, (4 of 5) showed muscle atrophy. Inconsistent skin changes were seen; skin thicking (1 of 5) skin thinning (3 of 5). All MR imaging signs were highly reproducible.	"MR imaging was beneficial in the demonstration of soft-tissue abnormalities in patients with RSD. MR imaging may also help stage RSD, particularly stages 1 and 3."	Data suggest MRI is useful for diagnosing RSD, specifically in those patients with soft tissue abnormalities.
Todorović-Tirnanić, M 1995 (score 5.5)	Scintigraphy	Diagnostic	No mention of COI or sponsorship.	N =44. 44 patients with limb fractur	Mean age of 44 patients: 51 years, Female =	RSD.	bone scintigraphy and radiography in the	Delayed scintigrams of RSD showed typical appearance of diffusely particularly peri-articularly increased radioactivity in bones of the distal portions of the limbs. Scintigrams of control were characterized by	"Bone scintigraphy has a very high sensitivity (97%), positive predictive value (97%) and accuracy (95%), as	Data suggests bone scan is the preferred early diagnostic method for post fracture RSD compared to radipgraphy.

				e, (37 with RSD and Seven without RSD)	22, Male = 22.		early diagnosis of post-fracture reflex sympathetic dystrophy	symmetrical distribution of 99mTc-DPD in the distal portion of the injured and contralateral extremities. Increase in 99mTc-DPD noted only at the site of fracture in its immediate vicinity. Scintigraphy was positive in (36 of 37) RSD. Presence of "patchy" atrophy in the bones of the distal part of the affect limb was noted in (27 out of 37) RSD patients. In 10 RSD patients the findings were negative. The significance of the difference between scintigraphic and radiographic, as well as between the interpreters of the results ($p < 0.01$). In second clinical stage of RSD ($p > 0.05$) Between the interpreters of scintigraphic and radiographic findings in both RSD and control ($p > 0.05$). X2 test ($x2=2.17$; $df = 1$; $p > 0.050$) in difference in the occurrence of fracture with fragment dislocation between the RSD patients and control group. ($X2 = 3.94$; $df = 1$; $0.01 < p < 0.05$) in RSD occurrence between patients with and without fragment dislocation after fracture. ($X2 = 0.17$; $df = 1$; $p > 0.05$) in occurrence of RSD after fracture according to the sex of the patient. X2 test showed ($0.01 < p < 0.05$) between the results of RNS, blood pool scintigraphy and delay scintigraphy. RNA was falsely negative in (4 of 20) patients with RSD, blood pool scintigraphy was falsely negative in (1 of 20) while delayed scintigrams did not produce any false negative results. RNA, blood pool and delayed scintigrams were negative in all control subjects.	well as a high specificity and negative predictive value, in the diagnosis of RSD after fracture. In comparison with radiography, bone scintigraphy proved to be the more sensitive, more specific and more accurate method. It has a higher positive and a markedly higher negative predictive value. It also provides insight into the condition of the complete skeletal system of the patient. The superiority of scintigraphy is most evident in the first clinical stage of RSD after fracture."	
Kock, E 1991 (Score 5.0)	Scintigraphy	Diagnostic	No mention of COI or	17 patients with	12 females, 5 males; No	Reflex sympathetic dystrophy.	Ti- and T2-	10 patient's completely normal findings. Bone marrow was abnormal in 3. Low signal intensity was noted on T1	appears to be of little value in establishing the	Data suggest MRI is not particularly useful for diagnosing RSD.

			sponsorship	reflex sympathetic dystrophy syndrome.	mention of mean age.		weighted MR Imaging of the affected body region.	and T2 weighted images. Third case showed diffuse decrease in signal intensity f the talus on T1 weighted and an increase on t2 weighted images. 3 patients showed soft tissue changes. One had edema, 2 had muscular atrophy. 2 showed join effusions in effected region. 8 patients who did not have RSD. 16 false-negative, 6 true negative, one true positive, two faulse positive cases, the sensitivity, specificity and diagnostic accuracy are 6%, 75% and 28% respectively.	diagnosis of sympathetic dystrophy, but may improve diagnostic specificity when used in conjunction with Scintigraphy.	
Werner, 1988 (score=4.0)	Scintigraphy	Diagnostic	No COI. Sponsored by Clinical Investigator Development Award (G.D.) from the National Institute of Neurological and Communicative Disorders and Stroke (NS 01120-20).	N=63 patients with nonspecific upper extremity pain.	Mean age:38±15 years. No mention of sex.	Reflex sympathetic dystrophy syndrome	RSDS with abnormal bone scan vs RSDS with normal bone scan	Patients with RSDS were on average 6 years older than others. Sensitivity, specifity, positive and negative predictive values were 50% in uptake phase to 38% in blood pool phase, 92% for both phases, 60% to 67%, and 81% to 84% respectively. Prevalence rate increased to 27%, but sensitivity, specificity, and predictive value did not change significantly. RSDS was diagnosed in 16 patients and abnormal TPBS in 8 patients. RSDS with abnormal TPBS had average symptoms for 2.4 months and average age of 50 years. RSDS and normal TPBS had symptoms on average for 18.9 months and average age of 31 years. (p=.07, .01 respectively) After restriction of dataset to patients with symptoms for less than 6 months sensitivity was 65%, specificity was 94%, positive predictive value of 88%, and negative predictive value of 79%. Patients include only above age 50 sensitivity increase to 100%, positive predictive value to 75%, and negative predictive value to 100%.	"The predictive value of the three-phase technetium bone scan was affected by the duration of symptoms and the age of the patient. Duration of symptoms less than 6 months, or ages more than 50 years substantially increased the sensitivity and positive predictive value of the three-phase technetium bone scan."	Data suggest the sensitivity and specifity of the three-phase technetium bone scan is dependent upon the duration of symptoms and patient age.

Davidoff, 1989 (score=4.5)	Scintigraphy	Diagnostic	Sponsored by Clinical Investigator Development Award (NS 01120-20) to Dr. Davidoff from the National Institute of Neurological and Communicative Disorders and Stroke. No COI.	N=119 patients with nonspecific limb pain.	Mean age: 35.1 years. 54 males, 65 females.	Reflex Sympathetic Dystrophy Syndrome	RSDS in upper extremity vs RSDS in lower extremity.	RSDS patients had shorter duration of symptoms between onset and date of TPBS (11.1 months vs 77.9 months; p<.05) and was an average of 10 years older. Of the 119 patients, 7 had diffusely asymmetric and abnormal blood-flow scan, 6 had diffusely asymmetric and abnormal delayed images, and 12 with abnormalities in all three phases. Sensitivity of blood-flow was 40%, specificity was 90%, positive predictive value was 53%, negative predictive value was 85%. When limb involvement was stratified decreased sensitivity and positive predictive value was observed for lower extremity RSDS.	"The results of this study suggest that for patients presenting with upper-extremity involvement, the three-hour delayed image may be an acceptable alternative to the more costly TPBS as an adjunct to the diagnosis of RSDS. In the case of patients with lower-extremity involvement, it would appear that the TPBS is indicated because of the improved sensitivity and specificity in diagnosing RSDS."	Data suggest comparable efficacy between tests and the uptake scan may be used for upper-extremity RSDS vs TPBS.
Wang, 1998 (score=4.5)	Scintigraphy	Diagnostic	No mention of sponsorship or COI.	N=30 patients with associated limb discomfort within 3 months onset of stroke.	Mean age: 63 years; 21 males, 9 females.	Reflex sympathetic dystrophy syndrome	RSDS in Right hemiplegia vs RSDS in Left hemiplegia	Positive delayed image of TPB demonstrated a sensitivity 92%, specificity of 56%, positive predictive value of 58%, and negative predictive value of 91%. Kappa statistic for positive bone scans and RSDS development was 70% (kappa=.43, p<.05). Male patients, patients with left hemiplegia or hemorragic stroke had higher incidence of RSDS.	"In conclusion, TPBS is a useful screening tool for development of RSD in hemiplegic patients. However, the diagnosis of RSDS depends on the clinical evaluative and the TPBS as an adjunct assessment of RSDS must be interpreted with caution.	Data suggest both clinical symptoms as well as bone scans are useful for screening RSDS in hemiplegic patients.
Kline 1993 (5.5)	Scintigraphy	Diagnostic	No reported COI from	8 patients with	mean age of 59.3 years; (4	Clinical diagnosis of Segmental	Clinical criteria vs scintigrap	The 8 patients in group 1 who met the strict criteria for segmental RSD were found to have a recognizable scan	"The vast majority of individuals with painful hand	Small sample. Data suggest earlier recognition of RSD via both clinical and

			all authors. No Mention of sponsorship	Segmental Reflex Sympathetic Dystrophy And consecutive bone scans (n=127) performed during 6 month period for upper extremity problems	males, 4 females)	reflex Sympathetic dystrophy and Segmentally diffuse pattern of tracer uptake in bone scans was found to be highly specific (98%) for segmental reflex sympathetic dystrophy.	hic criteria	pattern. Of the 127 sequential TPBSs evaluated to obtain specificity and predictive value data, 5 patients had a scintigraphic pattern consistent with segmental RSD. Two of these patients also had clinical findings and were included in group 1. One patient demonstrated segmental scintigraphic abnormalities of his thumb and carpal region. He was felt to have de-Quervain's disease. The bone scan was obtained to rule out scaphoid For statistical purposes he was considered to have a false positive result for segmental RSD. The other two patients, also classified as false positive for segmental RSD, were clinically felt to have regional RSD. They had more intense segmental tracer uptake superimposed on the diffuse pattern of regional RSD. One of these patients had rheumatoid arthritis. She had severe middle finger pain and swelling superimposed on more diffuse changes compatible with regional RSD. The other patient demonstrated "radial-to-ulnar fade," a pattern of regional RSD with slight radial accentuation of tracer uptake. We incidentally had noted this pattern in other patients evaluated for regional RSD.	and finger injuries do not demonstrate the clinical or scintigraphic abnormalities demonstrated by the small group of patients in this series. However, when recovery is abnormally prolonged and symptoms are out of proportion to the clinical injury, the contribution of sympathetic dysfunction should be considered. Management of patients with sympathetically mediated pain syndromes requires accurate diagnosis of the sympathetic component of their disorder in addition to an exhaustive search for anatomic sources serving as a triggering mechanism"	scintigraphic data is beneficial for managing pain.
Genant, 1975 (score=4.0)	Scintigraphy	Diagnostic	No mention of sponsorship or COI.	N=9 patiets ns	Mean age: 57 years. 3 males, 6 females.	Reflex sympathetic dystrophy syndrome	Scintigraphy vs radiography, and Histopathology	Bone mineral analysis showed metacarpal thickness for 7 of 9 patients at 3.5mm compared to 4.59 for uninvolved hands and 5.17 mm for controls. Both quantitative techniques indicate clinical less involved extremity demineralization. Joint and bone	"Aggressive patterns in bone resorption in reflex sympathetic dystrophy have been defined and characterized by fine-detail radiography.	Small sample size. Data suggest RSDS is a symptom complex of radiographic, scintigraphic, and histologic findings.

								scintigraphic findings showed an increased sensitivity. Histopathological exams showed edema, fibrosis, capillary proliferation in some of the findings.	The arthropathy of this disorder has been documented by a composite of radiographic, scintigraphic, and histological manifestations."	
Handa R 2006 (4.0)	Scintigraphy	Diagnostic	No mention of COI or sponsorship	Fourteen patients with reflex sympathetic dystrophy syndrome.	Mean age of 49.1, (8 male, 6 female)	Clinical features included extremity pain (100%), vasomotor symptoms (79%), hyperalgesia (72%), allodynia (36%), sudomotor symptoms (14%) and motor dysfunction (14%). Radiologic features included osteopenia (50%) and soft tissue swelling (7%).	Clinical criteria to diagnose CRPS vs. radiography (Bone scintigraphy)	As many as 43% of patients exhibited normal radiographs. Technetium 99 m 3-phase bone scintigraphy was abnormal in all patients in our series. Eleven of the 14 patients exhibited symptomatic response to nonsteroidal anti-inflammatory drugs and corticosteroids	"Reflex sympathetic dystrophy syndrome is a pain syndrome occasionally encountered by rheumatologists. Extremity pain is the most common presenting feature. Bone scintigraphy is very useful in corroborating the diagnosis even when radiographs are normal."	Small sample. Data suggests bone scintigraphy is useful for confirming a diagnosis of RSD in lien of negative radiography
Mackinnon S 1983 (score=5.5)	Scintigraphy	Diagnostic	No mention of COI or sponsorship.	N = 145 bone scans 102 of these were	Mean age of 23 patients: 43 years, Female = 12, Male = 11.	postsurgical or posttraumatic patients with pain who had definite RSD.	Three phase radionuclide bone scanning vs. clinically	Detailed analysis of the 145 three-phase radionuclide bone scans of the hand demonstrated that the diffuse increased tracer uptake in the delayed image (phase III) is diagnostic for RSD, with a sensitivity of	"Although a clear understanding of the pathogenesis of RSD and of the mechanisms of tracer uptake is still lacking, the TPBS remains	Data suggest use of delayed bone scans is sensitive to early diagnosis and then treatment of RSD.

				performed to evaluate pain in the hand, of these 23 patients clinically had reflex sympathetic dystrophy			diagnosed RSD	96% and a specificity of 98%. The two early phases (radionuclide angiogram and blood pool) were positive in only 45% and 52% of the RSD patients, respectively.	useful as a diagnostic indicator for patients suspected of having RSD and thus may help facilitate both the early diagnosis and the treatment of this significant problem."	
Kwon 2010 (5.0)	Scintigraphy	Diagnostic	No COI. No mention of sponsorship	Total 140 patients with/without CRPS1	mean age of 39±15 years, Female = 60, Male =80.	CRPS-1 (n=79), non CRPS (n=61)	Three-phase bone scan (TBPS)	Both increased and decreased periarticular delayed uptake image patterns (DU) were significant image findings for CRPS-1 (CRPS-1 positive-rate=73% in the increased DU group, 75% in the decreased DU group). The TIevent-scan did not differ significantly between the different image pattern groups. Quantitative analysis revealed an LCR of 1.43 was the optimal cutoff value for CRPS-1 and diagnostic performance was significantly improved in the increased DU group (area under the curve=0.732). Given the modified image criteria, the sensitivity and specificity of TPBS for diagnosing CRPS-1 were 80% and 72%, respectively.	"Optimally modified TPBS image criteria for CRPS-1 were suggested using image pattern and quantitative analysis. With the criteria, TPBS is an effective imaging study for CRPS-1 even with the most recent consensus clinical diagnostic criteria"	Data suggest TPBS is an effective imaging study for CRPS 1

Holder L 1984 (5.0)	Scintigraphy	Diagnostic	No mention of COI or sponsorship	Twenty-two of 23 patients with clinical criteria for RSD	Mean age and gender not specified.	Twenty-three patients with reflux sympathetic dystrophy were characterized as having complaints of diffuse hand pain. diminished hand function, joint stiffness, and skin and soft tissue trophic changes with or without vasomotor instability.	Three phase bone scanning (TPBS)	145 consecutive patients, 23 of whom had clinical RSD, underwent three phase radionuclide bone scanning (TPBS). Specific patterns for positive radionuclide angiogram, blood pool, and delayed images	"We concluded that TPBS could provide an objective marker for RSD, and it could also be used to exclude RSD in patients who had less specific signs and symptoms."	Data suggest TPBS may provide an objective marker for RSD to better determine the diagnosis of RSD in those patient with less specific symptoms.
Park 2007 (4.5)	Scintigraphy	Diagnostic	Sponsored by a research fund and Dankook University in 2005. No mention of COI.	N=38, 26 patients who were post stroke with acute CRPS and 12 healthy controls.	25 males, 13 females; mean age in CRPS patients: 57.5±11.6. Control patients: 46.8±18.8.	CRPS was diagnosed clinically using the criteria from International Association for the Study of Pain (IASP) in 1994.	Three Phase Bone Scintigraphy (TPBS) readings including vascular, blood pool, and delayed phase between healthy controls (N=12) vs. CRPS patients (N=26).	Sensitivity of Vascular phase 42.3%, blood pool phase 50%, delayed phase 65.4%. Combination of positive findings revealed a 80.8% sensitivity, and 100% specificity.	"In summary these findings suggest that a combined quantitative evaluation of each TPBS phase can improve the diagnostic strength of the very acute stage of CRPS after stroke."	Population is stroke patients. Data suggest a combination of TPBS phases may improve he diagnostic strength of the acute stage of CRPS post stroke.

Zyluk 1999 (4.5)	Scintigraphy	Diagnostic	No mention of sponsorship or COI.	N=100 patients with RSD and healthy controls.	28 males, 72 females; Mean age for RSD patients: 57 & Control patients: 58.	RSD diagnosis was made using 4/5 positive clinical indicators (diffuse pain, swelling, discoloration of the hand, abnormal skin temperature, limited range of motion (ROM).	Comparison TPBs in phase 1 (P1) which included metacarpal/carpal bones. In phase 2 metacarpal area (P2-hand), wrist area (P2-Wrist), and Phase 3 metacarpophalangeal joints of all four fingers (P3-MPJ), metacarpal bones in all four fingers (P3-MB), carpal bones (P3-CB) in RSD patients (N=70) vs Healthy Controls (N=30)	Uptake ratios control vs RSD patients phase 2 P2-hand RSD vs control patients, sensitivity & specificity: 40% & 60% vs 73% & 27% ($p<0.005$). P3-MPJ RSD vs control, sensitivity & specificity: 36% & 64% vs 80% & 20% ($p<0.0001$). P3-MB RSD vs control sensitivity & specificity: 20% & 80% vs 67% & 33% ($p<0.0001$). Uptake ratios varied significantly in duration of RSD as well as type of injury all phases ($p<0.005$).	"The results of our study, based on quantitative evaluation of TPBS, showed that this technique may be used only as an additional test in the diagnosis of RSD, with a sensitivity and specificity of 80%."	Data suggests that the diagnostic strength of TPBS to detect RSD is significantly associated with disease duration and type of RSD.

Intenzo 1988 (4.0)	Scintigraphy	Retrospective Diagnostic	No mention of sponsorship or COI.	N=32 patients with clinically confirmed RSDS.	8 males, 24 females; Age range 14-57.	Diagnosed with RSDS using clinical items (physical exam, history, signs and symptoms etc.)	Comparison between patients within stages I (N=8), II (N=21), and III (N=3) RSDS. Periarticular activity between symptomatic and asymptomatic contralateral extremities.	Periarticular increased activity, Stage 1, 2,and 3 ((N) (%)): Stage 1 patients: 2 had increased activity (25%), 6 normal (75%). Stage 2: 14 increased activity (66%), 4 decreased (20%), and 3 normal (14%). Stage 3: 3 had increased activity (100%). In summary, 72% Sensitivity.	"The authors conclude that bone scintigraphy is more likely to be positive in the later clinical stages of reflex sympathetic dystrophy of the lower extremity"	Data suggest bone scans are likely to yield positive findings for confirming RSDS in the lower extremities in later stages of the disease process.

Non-specific Inflammatory Markers for Screening for Inflammatory Disorders

Recommended.

Erythrocyte sedimentation rate and other inflammatory markers are recommended for screening for signs of systemic inflammation, particularly in assessing patients with ill-defined pain conditions.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications:	Undiagnosed patients with symptoms consistent with either systemic rheumatological diseases and/or patients have had incomplete evaluations. Subsequent, additional tests may be needed, including rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.
Benefits:	Diagnosing an unknown condition. Opportunity to prevent joint destruction.
Harms:	Negligible
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated with a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.
Rationale:	There are no quality studies evaluating the utility of C-Reactive protein, erythrocyte sedimentation rate, and other non-specific inflammatory markers for the diagnosis of patients with CRPS. Erythrocyte sedimentation rate is the most commonly used systemic marker for non-specific inflammation and is elevated in numerous inflammatory conditions as well as with infectious diseases. C-reactive protein is a marker of systemic inflammation that has been linked with an increased risk of coronary artery disease. However, it is also a non-specific marker for other inflammation. Other non-specific markers of inflammation include ferritin, and an elevated protein-albumin gap, however those two markers appear to have no known clinical roles. CRP and ESR measurements are minimally invasive, have low risk of adverse effects and are low cost. They are recommended as a reasonable screen for systemic inflammatory conditions especially in patients with chronic pain without clear definition of a diagnosis or those with myofascial pain syndrome, although the specificity is not high. **However, ordering of a large, diverse array of anti-inflammatory markers without targeting a few specific disorders diagnostically is not recommended.**
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome,

CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. There are no quality studies evaluating non-specific inflammatory markers for the diagnosis of patients with CRPS.

Cytokine Tests for Diagnosing CRPS and Chronic Pain

Not Recommended.

Routine testing with or the use of batteries of cytokine tests is not recommended to diagnose CRPS and chronic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:

Cytokines purportedly determine whether a patient is experiencing pain or has suffered a toxicological insult. However, there are no quality studies that address this premise especially in CRPS patients. Available studies suggest that these markers may be elevated in chronic pain conditions, but these studies did not have adequate control groups and did not control for potential confounders. The range of disorders in which cytokines may be elevated also needs definition, as the current range of conditions appears large,[149-157] suggesting they are not specifically isolated to patients with chronic pain, and thus the specificity of these tests seems likely to be quite low.

A high-quality, 7-year study of 880 elderly subjects evaluated impacts of IL-6 and CRP on both cross-sectional associations with morbidity and long-term mortality [149]. CRP and IL-6 were higher among smokers at baseline and those with higher body mass indexes (BMIs). IL-6 and CRP were also higher among those with hypertension, myocardial infarction, stroke, elevated glycosylated hemoglobin levels, HDL, and number of chronic conditions. Both IL-6 and CRP were inversely related to quartiles of moderate and strenuous physical activity. CRP and/or IL-6 were associated with incidence of hypertension, myocardial infarction, diabetes, and incident cases of chronic conditions. Physical performance measures of changes in grip strength, signature time, chair-rise and 6-m fast walk all were not significant for IL-6 or CRP. Cytokines need to be rigorously studied to ascertain if there is a place for them in the evaluation and/or

management of chronic pain conditions, including stratification for occupationally-relevant diseases. Documentation that the discovery of elevated cytokine levels results in changes in evaluation and/or clinical management would also be necessary. Alternatively, this testing may be useful if the absence of elevated cytokine levels would warrant concluding that a patient does not have a remediable physical cause of pain. While cytokine testing is minimally invasive, and has a low risk of adverse effects, these tests are high cost, with no evidence that they alter the clinical management of patients with chronic pain. Their place in the evaluation of patients with chronic pain is yet to be determined and cytokine testing is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. There are no quality studies evaluating non-specific inflammatory markers for the diagnosis of patients with CRPS.There is 1 high-quality study incorporated into this analysis. There is 1 low-quality study in Appendix 4 [158]. There are no quality studies evaluating cytokine tests for the diagnosis of patients with CRPS.

Surface EMG for Diagnosing CRPS and Chronic Pain

Not Recommended.

Surface EMG is not recommended for the differential diagnosis of CRPS and chronic pain. There are selective indications for use with biofeedback.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: Surface EMG has no demonstrated value in the clinical evaluation or treatment of CRPS with resultant altered management or improved clinical outcomes. Surface EMG may be of use in biofeedback training, and gait analysis for musculoskeletal and/or neurologic disorders, but it has no established use in the management of CRPS.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date

limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. There is one high quality study evaluating sEMG for the diagnosis of patients with chronic pain.

Evidence for Surface EMG

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Taaffe 2005 (score = 8.0)	Surface EMG	Prospective Cohort Study	No mention of Sponsorship or COI.	N = 880 age 70-79 participants in MacArthur Study of Successful Aging	Mean Age: 74.3 ± 2.7 years Sex (M:F) 412:458	Plasma IL-6, CRP levels determined by enzyme-linked immunosorbent assay and log transformed to normalize distributions. Physical function measures: handgrip strength, signature time, chair stands, 6-m walk time.	7 years	Women had lower ($p < 0.05$) IL-6 levels. Hours per year undertaking moderate and strenuous physical activity also related to inflammatory markers with higher ($p < 0.001$) IL-6 and CRP levels in less active individuals.	"Although IL-6 has been shown to predict onset of disability in older persons and both IL-6 and CRP are associated with mortality risk, these markers of inflammation have limited associations with physical performance, except for walking measures and grip strength at baseline, and do not predict change in performance 7 years later in a high-functioning subset of older adults."	Baseline IL-6 and CRP not associated with change in performance.

Functional MRIs for Diagnosing CRPS

Not Recommended.

Functional MRIs are not recommended for diagnosing CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies indicating that the findings on fMRIs are of sufficient sensitivity and specificity to permit identification of the presence or absence of CRPS. The clinical applications of the test have not been defined. Functional MRI is minimally invasive and has low adverse effects, but is high cost.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.There are no quality studies evaluating fMRI for the diagnosis of patients with chronic pain.

Local Anesthetic Injections for Diagnosing CRPS

Recommended.

Local anesthetic injections are selectively recommended for evaluations in CRPS patients.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	Chronic persistent pain in a specific nerve distribution (e.g., ilioinguinal, genitofemoral) that is otherwise unexplained by other investigation, including imaging, EMG/NCS. See TBI Guideline for guidance regarding occipital nerve blocks.
Benefits:	Potential to identify a potentially treatable lesion
Harms:	Medicalization, nerve trauma, and continuing a search for a fixable lesion if one is not to be found.
Frequency/Dose/Duration:	Once.
Rationale:	Local injections (including greater occipital nerve blocks, ilioinguinal, genitofemoral nerve blocks) have not been evaluated in sizable, quality studies for diagnostic, prognostic, or treatment purposes, though they may assist with diagnosis and consideration of potential treatment options and are thus selectively recommended. **However, corticosteroid or neuroablative injections/procedures for localized pain for these nerve blocks are not recommended as the risk of**

increased pain, local tissue reaction, and neuroma outweigh documented benefits (see Table 8).

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.There are no quality studies evaluating local anesthetic injections for the diagnosis of patients with chronic pain.

Table 8. Adverse Effects of Injections

General complications of neuraxial injections, and of injections near the paravertebral muscles	Infection at site and remote (meningitis found in one German study following trigger point, facet, and epidural injections). Bleeding, including hematoma causing nerve compromise. Direct trauma to nerve, causing permanent damage or increased pain. Injection into the wrong space (artery, vein, inadvertent intrathecal, or thoracic cavity). This can lead to respiratory compromise, cardiac arrest, or pneumothorax.
Complications specifically related to the substance and amount injected (in addition to possible anaphylaxis)	Local anesthetics – seizures, cardiac collapse. Sympatholytics – hypotension, tachycardia, cardiac dysrhythmias. Corticosteroids* – endocrine dysfunction, diabetes, hypertension, dysphoria, immune compromise, phlebitis, muscle pain, osteoporosis, dependency, rarely nerve damage, etc. Baclofen* – anxiety, blurred vision, ataxia, coma, depression, dizziness, dysarthria, dystonic reaction, hallucinations, headache, respiratory depression, seizures, stroke, etc. Botulinum toxins – weakness, paralysis, respiratory compromise, diplopia, dizziness, injection site reaction.

*These adverse effects are mostly temporary aggravations and dependent on dose and frequency.

QSART has been used for evaluation of CRPS patients [324, 325][326][327][328].

QSART for Diagnosing CRPS

No Recommendation.

There is no recommendation for or against the use of QSART to assist in the diagnostic confirmation of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality studies of QSART that evaluate patients with CRPS. There is a small-scale study evaluating QSART to detect abnormal responses in CRPS patients which suggested it may be successful.[325] This does not allow for evidence-based conclusions to be made regarding QSART's sensitivity, specificity or predictive value in making the diagnosis of CRPS when the clinical presentation does not support it. QSART is not invasive, does not have significant adverse effects, but is costly. As bone scans may demonstrate osteopenia or osteoporosis (which may develop in patients with CRPS) bone scans appear preferable to QSART. Bone scans are currently used for that purpose and in the absence of any quality head-to-head comparison of these tests, or adequate data regarding the sensitivity and specificity of QSART for this purpose, there is no recommendation for or against its use. Objective, quality evidence is needed to ascertain whether QSART may have utility in select situations where there is diagnostic uncertainty.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.There are no quality studies evaluating QSART for the diagnosis of patients with chronic pain.

SPECT/PET for Diagnosing Chronic Pain

Not Recommended.

SPECT is not recommended to evaluate patients with CRPS (aside from use in cases of suspected inflammatory arthropathies not diagnosed by more common tests). The use of PET scanning is also not recommended to evaluate patients with CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: SPECT and PET scanning have no quality evidence of efficacy in evaluation of CRPS patients. SPECT and PET scanning of the brain may be of use in assessing the status of cerebrovascular perfusion, tumors, and neurodegenerative conditions, but aside from providing information of interest for research, these techniques have not been shown to be useful in influencing the management of patients with

CRPS. PET scanning is expensive and SPECT scanning is moderately so. Both are mildly invasive. SPECT scanning may be useful in detecting inflammatory disease in the spine and other areas that might not be amenable to evaluation by other studies. There is no quality evidence of efficacy to support the use of SPECT or PET scanning for diagnosing CRPS.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus, 2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. There are no quality studies evaluating SPECT or PET for the diagnosis of patients with CRPS.

Thermography for Diagnosing CRPS

Not Recommended.

There is no recommendation for or against thermography for diagnosing CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: Thermography has been evaluated in 3 moderate quality studies of CRPS patients. The existing studies are small in size, with controls frequently outnumbering cases. Thermography has been demonstrated to be able to quantify temperature differences. However, more than a large proportion (often higher than 50%) of patients do not have significant temperature differences. Thus, provoking temperature differences through heating or cooling the extremity has been tried. Thermography has no quality evidence of benefits over various inexpensive devices (non-contact infrared thermometer) may also be effectively utilized to easily measure limb temperature differentials. Thermography is not invasive, has no adverse effects, is moderately costly but does not have clear evidence of efficacy and is thus not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, CRPS, reflex dystrophy syndrome; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 1,128 articles in PubMed, 385 in Scopus, 762 in CINAHL, 22 in Cochrane Library, 1,210 in Google Scholar, and 57 from other sources. We considered for inclusion 56 from PubMed, 8 from Scopus,

2 from CINAHL, 6 from Cochrane Library, 7 from Google Scholar, and 5 from other sources. Of the 84 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria. There are moderate-quality studies that evaluate thermography in CRPS patients.

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Niehof, 2006 (score=4.5)	CRPS	Diagnostic	The project is supported by a grant from the Dutch government (BSIK03016) and the Algesiological Research Foundation, Erasmus MC Rotterdam.No COI.	12 patients with CRPS I.	12 patients, (11 women and 1 man) with a mean age of 51.5 years	Complex Regional Pain Syndrome type 1	Thermography imaging during high and low whole body cooling and warming	The temperature difference between the hands in the CRPS patients increases significantly when the sympathetic system is provoked. At both the maximum and minimum vasoconstriction no significant differences were found in fingertip temperatures between both hands.	"The majority of CRPS1 patients do not show maximal obtainable temperature differences between the involved and contralateral extremity at room temperature (static measurement). During cold and warm temperature challenges this temperature difference increases significantly. As a result a higher sensitivity and specificity could be achieved in the diagnosis of CRPS1. These findings suggest that the sympathetic efferent system is involved in CRPS1."	Small sample. Data suggest baseline fingertip temperature measurements should not be used exclusively for diagnosing CRPS I.
Krumova 2008 (score=6.0)	CRPS	Diagnostic	Supported by Bundesministerium fur Bildung und Forschung (BMBF) Grants 01EM0107	N = 22	Mean age is 53 years; 6 males,	CRPS	Skin temperature, oscillation	Specificity of 67% for patients with pain 79% for healthy	"The applied skin temperature analysis can be easily applied in the	Data suggest skin temperature measurement can be a useful

			and 01EM0502 (German Research Network on Neuropathic Pain, DFNS). No COI.		16 females.		number, assessed time.	controls/ Sensitivity of 73% and 94% respectively.	clinical settings and serves as a further facet in the difficult diagnosis of CRPS."	diagnostic tool in management as well as diagnosis of CRPS.
Niehof 2008 (score=6.5)	CRPS	Diagnostic	Supported by Dutch Government grant (BSIK03016). No mention of COI.	N = 24	Mean age is 56 years; 7 males, 17 females.	CRPS	Hand or foot temperature, finger and to temperature, wrist and ankle temperature.	Sensitivities: Hand/feet 48%, finger/toe 67%, wrist/ankle 63%. Specificities: hand/feet 64%, finger/toe 57%, wrist/ankle 78%.	"The validity of skin surface temperature recordings under resting conditions to discriminate between acute CRPS1 fracture patients and control fracture patients with/without complaints is limited, and only useful as a supplementary diagnostic tool."	Data suggest limited validity with use of skin surface temperature in discriminating acute CRPS I patients from controls and should be used in combination with other CRPS diagnostic tools.

Treatment Recommendations

Activity Modification and Exercise

Bed Rest for CRPS

Not Recommended.

Bed rest is not recommended for CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – High

Rationale:	There is no evidence that bed rest is helpful for these conditions and it has been found to be unhelpful for LBP. There are potential adverse effects that reportedly have included pulmonary emboli (see Low Back Disorders guideline). Bed rest, although non-invasive, is costly, has no documented benefits, and is associated with higher morbidity, thus it is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating bed rest for the treatment of chronic pain syndromes. There are 11 high- or moderate-quality RCTs regarding bed rest for LBP incorporated into the guideline on Low Back Disorders.

Aerobic Exercise

Recommended.

Aerobic exercise is recommended for treatment of CRPS.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Moderate

Indications:	All phases of CRPS. Consider aquatic therapy if largely or completely non-weight bearing status (see below). However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's *Guidelines for Exercise Testing and Prescription,* 9th ed.,[161] in regards to health screening and risk stratification.

Benefits:	Improved function, improved endurance, improved return to work status.
Harms:	Negligible. Intolerance of weight bearing in severe lower extremity osteoarthrosis. Other musculoskeletal disorders possible (e.g., plantar heel pain).
Frequency/Dose/Duration:	Start with 3 to 4 visits a week to also include other exercises; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Simultaneous home exercise prescription. Transition to home-based exercise program. Target minimum of 30-45 minutes/day at one time. When at 30-45minutes, increase pace.
Indications for Discontinuation:	Short of developing a severe disorder (e.g., myocardial infarction), there is no reason to discontinue an aerobic exercise prescription. Consider altering the method(s) for non-tolerance, failure to progress, or reaching a 4 to 6 week timeframe.
Rationale:	There is no quality evidence that aerobic exercise is helpful for treatment of CRPS. There is one low quality trial suggesting aerobic exercise is of additive benefit for treatment of stroke patients with CRPS [331]. Yet, weight-bearing exercise may likely be the single best therapy for lower extremity CRPS. Weight-bearing exercise generally involves arm swing as well as conditioning/endurance, thus likely helpful for upper extremity CRPS. Aerobic exercise is not invasive, has negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, has strong rationale for treatment of CRPS patients, and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies incorporated into this analysis. There is one low quality RTCs in Appendix 4.

Strengthening Exercises

Recommended.

Strengthening exercise is recommended for treatment of CRPS.

Strength of Evidence – Recommended, Insufficient Evidence (I)
Level of Confidence – High

Indications:	All CRPS patients.
Benefits:	Resolution of CRPS, improved function, reduced pain, improved strength, improved ability to perform strength-demanding job tasks

Harms:	Negligible. Increased pain complaints as the strength demands are increased, yet the increased strength capacity is usable to document progress for the patient
Frequency/Dose/Duration:	Typically start with 3 to 5 visits a week, with more visits for those more severely affected. Most severe CRPS patients will require daily treatments at first to encourage increased activity, progress exercises and address fear avoidant beliefs ("kinesiophobia"). Mild to moderate cases may be reasonably treated twice to three times weekly. Should have demonstrable evidence of functional improvement within first 2 weeks to justify additional visits. Supervised treatment frequency and duration is dependent on symptom severity and acuity and the presence of comorbid conditions. Transition to including home exercises. Even in severe cases, active treatment regimens are recommended to be initiated at the first appointment (sometimes termed "stress loading"), merely supplemented with passive modalities as indicated.[314] Those initiating treatment may well have increased symptoms for the first few days of treatment, however pain and edema should decrease within a few days. It is believed to be critical for the entire treatment team as well as the family to be aware of this and to continue to encourage the patient to continue to progress, rather than decrease or eliminate active program elements. There are many potential strengthening exercises and these are believed to be the most important programmatic elements in the treatment of a CRPS patient.[128] A few examples of these activities include scrubbing, repeated forceful grasp, carrying of progressively heavier objects, distance walked, and repeated toe raises. Patients should be instructed that strengthening exercises are the most important aspects of the treatment program,[128] such exercises should be initiated at the first appointment, and home exercises should be strongly encouraged. It may be particularly helpful to monitor and graph the patient's progress through treatment sessions to demonstrate graphically that the endurance of pain is having meaningful benefits and used for motivational benefit. Activities that can be graphed include grip strength, amount or time of weight carry, time of scrubbing activity, numbers of repeated toe raises, and/or distance walked.
Indications for Discontinuation:	Non-tolerance, failure to progress, development of another disorder (e.g., strain), or reaching a 4 to 6 week timeframe.
Rationale:	There is no quality evidence that strengthening exercises as a stand-alone intervention are helpful for treatment of CRPS, although strengthening exercises are believed to be the most important therapeutic intervention for CRPS. One moderate quality trial suggested graded exercise is effective for CRPS (de Jong 05). Another trial found mostly comparable results between graded exercise and intentional exposures to painful stimuli that included forced, progressive use [332]. There is evidence that progressive exercises are beneficial for CRPS, and graded exposure to feared activities is beneficial for individuals with pain-related fear.[333] Despite the absence of quality evidence, the widespread acknowledgement of the criticality of exercise regimens is underscored by the inclusion of exercises in the treatment arms of many RCTs of CRPS.[118, 128] Thus,

exercise and therapeutic modalities are believed to be highly important in the treatment of CRPS patients.

The single most important method to manage edema is believed to be mobilization, rather than passive therapeutic modalities. The sooner the patient begins to use the extremity normally, the sooner the edema will resolve. There is no evidence that manual techniques and appliances to reduce edema are effective. Instead, they may take the focus away from the active treatment program, instead spending precious time on passive treatment. Edema management should be utilized in rare circumstances where there is a functional deficit or secondary vascular changes directly from the edema (see below). Otherwise, the focus and time in therapy should be spent on active therapies dealing with progressive active range of motion and strengthening exercises which indirectly treat the edema as well.

Strengthening exercises are not invasive, have negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, have strong rationale for select indications, and thus are recommended.

Evidence:

Complex Regional Pain Syndrome – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 34 from other sources. We considered for inclusion 23 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 34 from other sources. Of the 62 articles considered for inclusion, 57 randomized trials and 37 systematic studies met the inclusion criteria. There are moderate-quality RCTs or crossover trials incorporated into this analysis.

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Length of Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Lee 2002 (score = 7.5)		RCT	Supported by a grant from the National Institutes of Health/National Institute of Child Health and Human Development. No mention of COI.	N = 28 with CRPS recruited from a children's hospital in Boston	Mean age: Group A: 12.5 ± 2.2 Group B: 13.3 ± 2.8 Sex(M:F) 2:26	Low frequency(n = 15, once a week, 6 weeks) PT vs. high frequency (n = 13, 3 times week for 6 weeks). Both interventions received cognitive behavioral therapy.	Follow up at 6 weeks to 3months and 6-12months.	At end of study, pain scores were median 0, CRPS recurrences 38% low frequency vs. 64% high frequency and 67% (low frequency) vs. 70% (high frequency) participated in sports.	"Compliance with attendance of PT sessions was good in both groups, and there was no apparent difference between a group of individuals receiving 6 PT sessions and those receiving 18 sessions."	Pediatric population, may not apply to adults with CRPS. No between-group differences at baseline or follow-up. Improvements maintained.
Oerlemans 1999, 2000 (score = 7.0)		RCT	Supported by by a grant from National Health Insurance Board. No mention of COI.	N = 135 with upper extremity CRPS-I of 1 upper extremity (<1 year duration) in Netherlands	Mean Age: 52.7 Sex(M:F) 30:70	PT (n = 44) vs. OT (n = 44) vs. social work (SW) control (n = 47). Pre-established protocol of free-radical scavengers, peripheral vasodilators in case of primarily cold RSD, treatment of trigger points.	*6 weeks, 3months, 6months, 12months.*	PT/OT/SW/PT-OT/PT-SW/OT-SW mean(SE) impairment-level subscores and components (per protocol analysis) for ISS, temperature, VAS, MPQ-DLV, volume, and AROM.	"[A]djuvant PT, and to a lesser extent OT, makes a variable contribution to the relief and cure of signs and symptoms of RSD."	Data suggest minimal differences. Authors attribute to lack of active rehab program.

De Jong 2005 (score = 5.0)		RCT	No mention of sponsorship or COI.	N = 8 who had CRPS Type I and reported substantial pain-related fear	Mean age: 40±10.2 Sex(M:F) 0:8	Single-case experimental ABC-design: a) BAS no treatment; b) EDU post-BAS then no treatment; Cc GEXP. Education intervention on Day 8 vs. 15; duration 7 vs. 14 days. No-treatment baseline then education then no-treatment. GEXP engaged in activities patients identified as fearful on graded basis. Education group received information on fear-avoidance behaviors.	*6 months*	Self reported signs/symptom differences across study periods for BAS vs. GEXP (p = 0.042), and BAS vs. follow-up (p = 0.039). Self reported signs and symptoms of CRPS (% positive) by group: hyperesthesia (BAS 100.0 vs. GEXP 0.0 vs. follow-up 0.0), edema (BAS 87.5 vs. GEXP 0.0 vs. follow-up 0.0).	"The GEXP was successful in decreasing levels of self-reported pain-related fear, pain intensity, disability and physiological signs and symptoms. These results support the hypothesis that the meaning people attach to a noxious stimulus influences its experienced painfulness and the GEXP activates cortical networks and reconciles motor output and sensory feedback."	Small sample size. ata suggest efficacy.

Gobelet 1986 (score = 4.0)		RCT	No mention of sponsorship or COI.	N = 24 with Stage I RSDS affecting extremities after trauma; severe pain, edema and hyperhidrosis	Mean Age: Group 1: 54 Group 2: 54.7 Sex(M:F) 11:13	PT (n = 12) vs. PT plus salmon calcitonin 100 MRC SQ units daily for 3 weeks (n = 12). PT 5 times a week for 3 weeks, then 3 times a week up to 5 more weeks. Controls received same PT.	*2 weeks, 8 weeks, 24 weeks*	Four of 12 (33%) from PT alone group vs. 6 of 12 (50%) from PT with calcitonin group fit for work at 8 weeks. Nineteen of 24 fit for work at 24 weeks.	"[T]he authors advocate the use of calcitonin in addition to physical therapy in reflex sympathetic dystrophy syndrome – and even of calcitonin alone where physical therapy is not possible."	Small sample sizes (12 each). Multiple co-interventions. Many details sparse. Data suggest calcitonin modestly effective as an adjunct to PT.
Barnhoorn 2015 (4.5)	Treatment	RCT	Funded by the Netherlands organization for health research and development (ZonMw) (grant number 170991004).	N = 56 with CRPS I. All had had stroke.	(11 males, 45 females); mean age is 44.3 years.	(N = 28) Pain Exposure Physical Therapy (PEPT) vs (N = 28) Conventional Treatment	*3,6, and 9 month follow-up.*	63 percent of the PEPT group achieved MCID compared to 56 percent in the conventional treatment (CONV) group (95% CI .72 to 1.77). The PEPT group had a decrease in ISS-RV of 6.7 points and 6.2 points for CONV (95% CI 1.56 to 3.48 p = 0.45). There was a significant difference for the AROM with a decrease in PEPT and CONV group (95% CI .07 to .94 p = 0.02). Greater improvement between treatment groups in favor of PEPT (95% CI .1 to 5.7; p = .04).	"We cannot state that PEPT is superior to CONV for patients with CRPS-1. However, patients allocated to PEPT did experience a greater improvement in AROM compared to those allocated to CONV."	Intervention is poorly defined and described. Intention to treat analysis yields only one statistically significant difference between treatment groups; range of motion.

Stretching Exercises

Recommended.

Stretching exercise is selectively recommended for treatment of CRPS.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	Severe, chronic CRPS. May be indicated especially if the patient avoids all use of the extremity. Otherwise, better options are progressive strengthening and mirror and image therapy. Consider aquatic therapy if largely or completely non-weight bearing status (see below).
Benefits:	Improved function, improved endurance, improved return to work status.
Harms:	Strengthening is believed to be superior, thus excessive time spent on flexibility may delay recovery. Careful supervision of the course of recovery is needed.
Frequency/Dose/Duration:	Start with 3 to 4 visits a week; advance exercises and demonstrate evidence of functional improvement. Quickly advance to inclusion of strengthening exercises, aerobic exercises, mirror or image therapy or other functional exercise. Simultaneous home exercise prescription. Transition to home-based exercise program.
Indications for Discontinuation:	N/A. Consider altering the method(s) for non-tolerance, failure to progress, or reaching a 4 to 6 week timeframe.
Rationale:	Although widely used, there are no quality studies that stretching exercise is helpful for treatment of CRPS. Among patients with severe pain and disuse of the extremity, flexibility exercises may be helpful to transition to other exercises (e.g., strengthening, image/mirror therapy, aerobic, yoga). Most patients with non-severe CRPS do not have meaningful reductions in range of motion and emphasis on range of motion is usually to the detriment of advancing more functionally important exercises, such as strengthening and aerobic or conditioning. The main indication for including stretching exercises is for select CRPS patients, often times the most severely affected, with meaningful reductions in range of motion for whom inclusion of flexibility exercises may be of benefit; still, stretching exercises should not be the sole exercise prescription for such patients. Stretching exercises are not invasive, have negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, do not have quality evidence for efficacy in CRPS patients, but are thought to be helpful in select patients with reduced range of motion and thus are selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from

other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating stretching exercise for the treatment of CRPS.

Mirror Therapy and Guided Imagery for CRPS

Recommended.

Mirror therapy is recommended for motivated patients with moderate and severe CRPS who are willing to comply with the treatment. There are other components of guided imagery which may be utilized.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Moderate

Indications:	Moderate and severe cases of CRPS. May be particularly helpful for those having difficulty complying with progressive strengthening exercises.
Benefits:	Accelerated progressive exercises and progressive use, with reduced need for medications
Harms:	Negligible
Frequency/Dose/Duration:	Home exercises requiring an estimated 10 minutes of each waking hour for 6 weeks. Best results obtained from viewing unaffected limb and performing activities as fast and accurately as possible with affected hand. Clinic appointments are needed and are estimated at least 3 times a week for 6 weeks in addition to home exercises. In the event of ongoing improvements and need for additional appointments, additional treatments to continue the therapy would be indicated in 2 to 3 week increments provided there was continuing objective evidence of ongoing improvement after each additional increment.
Indications for Discontinuation:	Resolution or sustained non-compliance. In the event of non-compliance, an evaluation is needed to assess motivational factors, secondary gain and related issues.
Rationale:	There are three moderate-quality studies suggesting efficacy of mirror therapy that have been performed by the same research group [334-336]. One researcher has suggested efficacy for treatment of stroke patients with CRPS [337], suggesting potential duplication of the prior study results. The intensity and type of involvement by the experimental group brings into question whether they were completely blinded. As well, reproducibility is a little unclear as most of the literature is from one research group. Thus, the strength of evidence rating was downgraded from "B" to "C" level evidence. The study results demonstrated a decrease in pain rating and improvement in numerical task rating scale. The benefits include evidence of subsequent reduction in need for health care treatment.[336] Mirror therapy is not invasive, has no adverse effects, is not costly, and with quality evidence of efficacy is recommended. The main difficulty is the requirement to comply with the exercises – 10 minutes of each waking hour.

Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria.There are moderate-quality RCTs or crossover trials incorporated into this analysis.[334-336] There is one low quality RTC in Appendix 4.

Evidence for the Use of Motor Imagery Programs

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Moseley 2004 (score = 7.0)	Motor imagery programs	RCT/Crossover Trial	This study was sponsored by a Clinical Research Fellowship from the National Health and Medical Research Council of Australia ID 210348. No mention of COI	N = 13 with CRPS Type I diagnosed by Bruehl criteria after complicated wrist fracture (>6 months duration)	Mean age: 36..5 years (9 females, 4 males)	Motor imagery program (MIP) consisting of hand laterality recognition task, imagined hand movements and mirror therapy vs. ongoing management. CRPS subjects chosen due to prior evidence that technique worked in acute CRPS I; medications remain unchanged. MIP group asked to perform their treatment for 10 minutes of each waking hour. Control group or waiting-list control asked not to change medication or dosage and to record any new treatments received. Treatment 12 weeks before crossover.	Assessments were repeated 2, 4, 6 and 12 weeks after the commencement of treatment of the 6-week program	After 6 weeks, 2 MIP-treated patients no longer met CRPS diagnostic criteria. After 12 weeks, control group crossed-over to MIP. Main effect of treatment group and an effect size of approximately 25 points on neuropathic pain scale. Effect of treatment replicated in crossover control subjects. Significant reduction in all 3 variables during MIP maintained for at least 6 weeks post treatment, $p < 0.01$.	"The results uphold the hypothesis that a MIP initially not involving limb movement is effective for CRPS I and support the involvement of cortical abnormalities in the development of this disorder."	Baseline differences in mean duration of CRPS somewhat favored MIP group (51 vs. 65 weeks). Score (7.0) based on RCT, but crossover results 6 weeks later further strengthen results. Study lends credence to concept that exercise is critical for recovery from CRPS.

Moseley 2006 (score = 6.5)	Motor imagery programs	RCT	No COI. No mention of sponsorship	N = 51 with CRPS Type I or phantom limb pain	Mean age not reported, gender not identified	Graded MIP with physiotherapy treatment (n = 25) vs. maintained usual medical care (n = 26); 37 of 51 had CRPS I (5 brachial plexus avulsion injury, 9 amputees of 1 limb). Intervention group received motor imagery program consisting of 2 weeks each of limb laterality recognition, imagined movements, and mirror movements. Control group received PT once a week, home therapy with training load, and ongoing medical care.	Follow up-6 month	In follow-up period, 100% of controls vs. 11 in intervention group sought treatment. Number needed to treat for 50% pain reduction or 4-point increase in function at 6 months was 2; 11 patients in treatment group vs. all in control group sought treatment for pain during follow-up period, p <0.001.	"Motor imagery reduced pain and disability in these patients with complex regional pain syndrome type I or phantom limb pain, but the mechanism, or mechanisms, of the effect are not clear."	Data suggest motor imagery effective for CRPS or phantom pain.

Moseley 2005 (score = 6.0)	Motor imagery programs	RCT	This study was sponsored by a Clinical Research Fellowship from the National Health and Medical Research Council of Australia ID 210348. No mention of COI	N = 20 with CRPS Type I diagnosed by Bruehl criteria after complicated wrist fracture (>6 months duration)	Mean age 34 gender not identified	Group 1, n = 7 (received hand laterality recognition, imagined movements, mirror movements) vs. Group 2, n = 6 (received imagined movements, recognition, imagined movements), or Group 3, n = 7 (received recognition, mirror movements, recognition) with 12 week follow-up.	Follow up at week 12	At 6 and 18 weeks, reduced pain and disability greater for Group 1 than other groups. Increase in task specific NRS more in Group 1 vs. 2 and 3, p <0.05 for both. At 12 weeks, reduction in total NPS and increase in task specific NRS greater for Group 1 vs. 2 or Groups 3, p <0.05 for both.	"Hand laterality recognition imparted a consistent reduction in pain and disability across groups, however, this effect was recognition. Imagined movements imparted a further reduction in pain and disability, but only if they followed hand laterality recognition. Mirror movements also imparted a reduction in pain and disability, but only when they followed imagined movements."	Best results obtained from viewing unaffected limb and performing activities as fast and accurately as possible with affected hand.

Vural 2016 (5.5)	Chronic, CRPS	RCT	No mention of conflict of interest.	N = 30 patients with first-time stroke and CRPS in the stage of dystrophy.	Mean age of 65.15, 13 females, 17 males.	Each group received patient-specific conventional stroke rehabilitation for 2-4 hours per day, 5 days a week for 4 weeks. The mirror therapy group (N = 15) received an additional 30 minutes per day of mirror therapy compared to control group (N = 15).	At baseline and after 4 weeks of therapy, the following assessments were performed: Brunnstrom recovery stages of the arm and hand for motor recovery, Fugl-Meyer Assessment (FMA, subsections of wrist and hand), FIM-motor for functional status (motor items only), Modified Ashworth Scale (MAS) (to measure Spasticity), and visual analog scale (VAS, to measure pain severity).	Compared to baseline, statistically significant results were seen in both groups for FIM-motor and VAS scores, with greater improvements in the mirror therapy group (P=.03, P=.01, respectively). Additional significant results were in the mirror group for Brunnstrom recovery stages (P=.01) and FMA (P<.001)	"This study demonstrates that in patients with stroke with CRPS type 1, addition of mirror therapy to a conventional physical therapy and rehabilitation program provides greater improvement in motor recovery and upper limb motor function of the paretic side. Mirror therapy is a noninvasive, inexpensive, and simple applicable rehabilitation modality with no significant complications. "	Significant difference in pain and function between groups. Conventional stroke comparison treatment not well described or reproducible, all stroke patients with mirror therapy adjuvant to poorly described standard stroke therapy.

Aquatic Therapy for CRPS

Recommended.

Aquatic therapy is recommended for patients with CRPS to develop increasing tolerance to graded activities.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Moderate

Indications:	Moderate to severe CRPS patients. Includes those with underlying morbidity making weight bearing problematic (e.g., severe lower extremity degenerative joint disease) or those who previously exercised by swimming etc. Particularly includes those with lower extremity CRPS that is severe with weight bearing difficulty. May also include those with severe upper extremity CRPS.
Benefits:	Improved function, reduced pain, resolution of the symptoms and signs of CRPS
Harms:	Initially increased pain while increasing strength, however this typically reduces with further progressive use. Water temperature may have to be fairly high for more severely affected CRPS patients.
Frequency/Dose/Duration:	Appointments initially 3 times a week, but 5 times a week if severe CRPS. Home exercises should be simultaneously prescribed.
Indications for Discontinuation:	Resolution, ability to maintain progressive increases without supervision.
Rationale:	There are no quality studies of aquatic therapy for treatment of CRPS. However, there is strong rationale for increasing activities as the primary treatment of CRPS and for some, weight bearing is problematic. Aquatic therapy is not invasive, has low adverse effects, is moderate to high cost in aggregate and is selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria.There are no quality studies evaluating aquatic therapy for the treatment of CRPS.

Desensitization Techniques for CRPS

Recommended.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Moderate

Indications:	Moderate to severe CRPS patients with significant hyperalgesia. Should be primarily engaged in a core program of graded strengthening exercises or for whom there is a plan to implement such exercises shortly after or in conjunction with desensitization techniques. (Desensitization techniques are unlikely to be successful for functional restoration and are not recommended as a sole exercise or therapy intervention.)
Benefits:	Improved function, reduced pain, resolution of the symptoms and signs of CRPS
Harms:	May experience some increased pain initially. However, this typically reduces with further progressive use. Susceptibility to view desensitization as the primary treatment instead of progressive strengthening.
Frequency/Dose/Duration:	Appointments initially 3 times a week, but 5 times a week if severe CRPS. Home exercises should be simultaneously prescribed.
Indications for Discontinuation:	Resolution, sufficient improvement to no longer require desensitization, ability to maintain progressive increases without supervision.
Rationale:	There are no quality trials consisting solely of desensitization techniques. Desensitization techniques are thought to be needed for severe cases of CRPS where there are significant problems with allodynic pain. Such techniques may include rubbing the extremity with progressively more textured materials and/or with more force. Contrast baths is a related therapy, however, exacerbation by cold water is common and this intervention is generally thought to not be particularly effective. Contrast baths are not indicated for nearly all CRPS patients; however, there may be a limited role in some patients.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is one moderate-quality RCTs incorporated into this analysis.There is 1 low-quality study in Appendix 4.

Desensitization Techniques for CRPS

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Length of Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Karlijn Barnhoorn (4.5)	Treatment	RCT	Funded by the Netherlands organization for health research and development (ZonMw) (grant number 170991004).	N = 56	(11 males, 45 females); mean age is 44.3 years.	(N = 28) Pain Exposure Physical Therapy (PEPT) vs (N = 28) Conventional Treatment	*3,6, and 9 month follow-up.*	63 percent of the PEPT group achieved MCID compared to 56 percent in the conventional treatment (CONV) group (95% CI .72 to 1.77). The PEPT group had a decrease in ISS-RV of 6.7 points and 6.2 points for CONV (95% CI 1.56 to 3.48 p = 0.45). There was a significant difference for the AROM with a decrease in PEPT and CONV group (95% CI .07 to .94 p = 0.02). Greater improvement between treatment groups in favor of PEPT (95% CI .1 to 5.7; p = .04).	"We cannot state that PEPT is superior to CONV for patients with CRPS-1. However, patients allocated to PEPT did experience a greater improvement in AROM compared to those allocated to CONV."	Intervention is poorly defined and described. Intention to treat analysis yields only one statistically significant difference between treatment groups; range of motion.

Yoga for CRPS

Recommended.

Yoga is selectively recommended for treatment of CRPS.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	Moderate to severe CRPS patients. Particularly indicated for those who are motivated and interested in yoga.
Benefits:	Improved function, reduced pain, resolution of the symptoms and signs of CRPS
Harms:	It could be used as a substitute for increasing strengthening exercises and conditioning and thus delay recovery.
Frequency/Dose/Duration:	Appointments initially 3 times a week, but 5 times a week if severe CRPS. Daily home exercises should be simultaneously prescribed.
Indications for Discontinuation:	Resolution, ability to maintain progressive increases without supervision.
Rationale:	There is no quality evidence for yoga to treat CRPS patients. There is moderate-quality evidence of the effectiveness of yoga for the treatment of chronic LBP,[163-165] although there are many different types of yoga and no study results have been replicated. Evidence also suggests that patient motivation must be high, and there is much self-selection in the reviewed studies, as compliance and adherence reportedly are not good. Yoga is not invasive, has low potential for adverse effects, is low cost, has no evidence of efficacy, but a few highly motivated patients may engage in and increase activity with yoga and thus it is selectively recommended. It should not substitute for increasing strengthening exercises and conditioning.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria.There are no quality studies evaluating yoga for the treatment of CRPS or trigger points/myofascial pain. There are 5 high- or moderate-quality RCTs incorporated into this analysis (see Low Back Disorders guideline for these studies).

Medications

NSAIDs have been used for treatment of CRPS.

Oral NSAIDs for CRPS

Recommended.

Oral NSAIDs are recommended for treatment of CRPS.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	CRPS sufficiently severe to require medication. NSAIDs are recommended as an adjunct to strengthening, conditioning and aerobic exercises. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as first-line medications. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious. Over-the-counter (OTC) agents may suffice and may be tried first. Second-line medications should include one of the other generic medications. COX-2 selective agents are recommended as a third- or fourth-line medications when there are contraindications for other NSAIDs and/or there are risks of GI complications; however, concomitant treatment with misoprostol, sucralfate, and proton pump inhibitors are also options for gastro-protection.
Benefits:	Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. NSAIDs are among the best medications especially for safety sensitive workers.
Harms:	Gastrointestinal adverse effects are especially prominent in those with past history of gastrointestinal bleeding, for which either cytoprotection or Cox-2 agents are advisable. Those elderly, with diabetes mellitus and rheumatological orders also are among those at increased risk. There is some evidence for increased cardiovascular risks, especially in the more Cox-2 selective NSAID agents. There is no clear evidence of cardiovascular harm from the non-selective NSAIDs ibuprofen and naproxen. (see further discussion in Low Back Disorders). It appears that despite widespread usage, diclofenac does not have clear superiority at least for LBP where it has been trialed, yet may have increased risks for adverse cardiovascular events.[188]
Frequency/Dose/Duration:	For most patients, scheduled dosage, rather than as needed, is preferred to avoid adverse effects of other treatment options, but prescribing NSAIDs as needed is reasonable for mild or moderate symptoms. Due to the potential adverse effects from chronic use (more than 2 months) of NSAIDs, patients should be periodically monitored for adverse effects such as hypertension, blood loss, renal insufficiency (as manifested by an increased creatinine), and hepatic enzyme elevations. Older patients and those with co-morbidities may require more frequent monitoring. Use of an adjunctive cytoprotective agent may also be warranted.
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale: There is no quality evidence of efficacy of NSAIDs compared with placebo for CRPS. Although there is evidence that a COX-2 inhibitor (parecoxib) is superior to placebo as part of an intravenous regional blockade that includes clonidine and lidocaine. There also is evidence that piroxicam is inferior to prednisolone for post-stroke CRPS Type I.[341] However, those results might not apply to other causes of CRPS and piroxicam is elsewhere found to be a relatively weak NSAID. NSAIDs are not invasive, have low adverse effects in employed populations, are low cost, have evidence of efficacy for many musculoskeletal disorders, and thus inferred for CRPS, and are thus recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating oral NSAIDs for the treatment of CRPS.

Acetaminophen for CRPS

Recommended.

Acetaminophen is recommended for treatment of CRPS particularly if NSAIDs are contraindicated.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications: CRPS sufficiently severe to require medication. Acetaminophen is recommended as an adjunct to strengthening, conditioning and aerobic exercises. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as first-line medications. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious.

Benefits: Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. Acetaminophen is among the best medications especially for safety sensitive workers.

Harms: Negligible if used as prescribed. Renal adverse effects are possible, especially among chronic, high-dose users and those with other renal impairment. Hepatic toxicity in high doses or among those with other

	hepatic impairments (e.g., excessive alcohol consumption). Reduced dosage may be used in such settings, along with close monitoring.
Frequency/Dose/Duration:	Generally prescribed up to 3.5g/day in divided doses, usually QID dosing
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.
Rationale:	There are no quality trials of acetaminophen for treatment of CRPS. Acetaminophen is not invasive, has very low adverse effects, is low cost, has evidence of efficacy for treatment of some musculoskeletal disorders and is thought to have modest efficacy and thus is recommended for treatment of CRPS.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating acetaminophen for the treatment of CRPS.

Intravenous NSAIDs for CRPS

Recommended.

NSAIDs are recommended as intravenous adjuncts for regional blockades that also include lidocaine and clonidine for treatment of CRPS.

Strength of Evidence **– Recommended, Evidence (C)**
Level of Confidence – Low

Indications:	Severe CRPS that has responded insufficiently to progressive strengthening exercises, aerobic exercises and oral medications, generally including bisphosphonates.
Benefits:	Improved pain control with ability to sustain progressive exercises
Harms:	Adverse effects related to either clonidine, lidocaine and/or NSAID. Includes hypotension, dysrhythmias.
Frequency/Dose/Duration:	Three injections at weekly intervals. The single quality study used: 30µg clonidine plus 1mg/kg lidocaine plus 0.9% saline solution plus 5mg parecoxib [342]. As parecoxib is not available in the US, other NSAIDs should be considered.
Indications for Discontinuation:	Adverse effects, reaching the end of the series of 3 injections.
Rationale:	There is one moderate quality trial suggesting an IV COX-2 inhibitor (parecoxib) is superior to placebo as part of an intravenous regional

	blockade that includes clonidine and lidocaine [342]. However, another moderate quality pilot trial in 20 patients suggested IV parecoxib BID for 2 days was not superior to placebo (Breuer 14). Intravenous regional blockades are invasive, have adverse effects, are moderate to high cost, have some evidence of efficacy when combined with clonidine and thus are selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria.

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Length of Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Kalita 2006 (score = 6.0)		[RCT, prospective, etc.]	No mention of Sponsorship or COI.	N = 60 with CRPS I following stroke	Mean age: 56 years Sex (M:F) 40:20	Prednisolone 40mg (n = 30) or piroxicam 20mg daily (n = 30) for 14 days.	1 month	Total CRPS score (initial/1 month): prednisolone (10.73±1.95/4.27±2.83) vs. piroxicam (9.83±2.34/9.37±2.89). Sensory: (3.97±0.85/1.13±1.31) vs. (4.00±0.87/3.67±1.35). Autonomic: (2.17±0.70/0.77±0.73) vs. (2.00±0.53/1.70±0.65). Humeral abduction: (2.30±0.70/1.27±0.87) vs. (2.03±0.85/1.97±0.93). Humeral extension rotation: (2.37±0.72/1.13±0.94) vs. (2.07±0.87/2.07±0.91). Barthel index (BI) score: (1.97±4.94/9.87±4.43) vs. (2.57±4.32/7.07±5.56).	"[A] short course of oral prednisolone significantly reduces the symptoms and signs of CRPSI following stroke compared to piroxicam, and both drugs improve the activity of daily living as assessed by BI score."	Stroke patients. In upper extremity CRPS I post-stroke prednisolone improves symptoms over piroxicam. After 1 month, no mention of co-intervention. Data suggest steroid superior to piroxicam.
Frade 2005 (score = 5.5)		RCT	No mention of Sponsorship or COI.	N = 30 with CRPS Type I in upper limb	Mean age: CG group 41, IVRAPG group 41, SPG group: 44. Sex(M:F) 13:17	30µg clonidine plus 1mg/kg lidocaine plus 0.9% physiologic solution (control, CG, n = 10) vs. 30µg clonidine plus 1mg/kg lidocaine plus 0.9% physiologic solution plus 5mg parecoxib (group IVRAPG,	3 weeks	VAS before/60 minutes after each intervention: CG Week 1 (8±1.15/2.6±1.9), Week 2 (5.9±1.1/1.5±0.97), Week 3 (5±1.66/2.1±1.97); IVRAPG Week 1 (8±1.56/2.4±2.67), Week 2 (5.8±2.4/1.2±1.98), Week 3 (3.1±1.66/0.6±1.26); SPG Week 1 (8.3±1.25/2.6±3.1), Week 2 (6±1.83/1.5±1.08), Week 3 (5±1.56/2.2±1.8), CG vs. SPG decrease Week 1 to 2. Mean daily oral ketoprofen consumption end of each week (1st/2nd/3rd week): CG	"[I]n contrast to IV systemic 20 mg of parecoxib, IV 5 mg of parecoxib was an effective coadjuvant combined with weekly clonidine/lidocaine loco-regional block for CRPS type 1."	Data suggest parecoxib may have additive benefit when combined with clonidine.

						n = 10) v. 30µg clonidine plus 1mg/kg lidocaine plus 0.9% physiologic solution (SPG, n = 10) 3 times at weekly intervals.		(180±92/150±97/170±106) vs. IVRAPG (170±106/60±70/70±80) vs. SPG (190±74/150±108/160±96), IVRAPG smaller consumption 2nd and 3rd week vs. other groups, p <0.05.		
Breuer 2014 (score=5.0)	CRPS	RCT	No COI. Supported by grant from the Ruhr University Bochum.	N = 20 with diagnosis of CRPS in the upper limb	10 female, 10 male. Mean age parecoxib group 46.5 years, placebo 51.0 years	40 mg of Parecoxib twice a day for two days (N = 10) vs 40 mg of placebo (NaCl 0.9%)	1 day after final injection	Pressure pain threshold (PPT) – Placebo (day 3 – day 0 change): -14.7 kPA, Placebo 26.5 kPA (difference not significant, P=0.6). Heat pain threshold (HPT) – Parecoxib 1.6°C, Placebo 0.7°C (P=0.29). Numeric Rating Scale for Pain – Parecoxib -0.6, Placebo -0.7 (P=0.32).	"In the present proof-of-concept trial, short-term treatment with the selective COX-2-inhibitor parecoxib influenced neither PPT nor edema or pain. COX-2 might be less important than previously assumed."	Small sample size (n=20) post hoc analysis of COX-2 with a short duration of follow up (2 days) no meaningful differences were observed between groups

Anti-depressants have been used to treat CRPS [343-346].

Norepinephrine Reuptake Inhibitor Anti-depressants for CRPS

Recommended.

Tricyclic anti-depressants (includes norepinephrine reuptake inhibitor anti-depressants) are recommended for treatment of CRPS.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	Chronic pain not fully treated with progressive strengthening, aerobic exercises and generally NSAIDs. May be particularly helpful if there is nocturnal sleep disruption and mild dysthymia, which may allow for nocturnal dosing of a mildly sedating tricyclic anti-depressant.
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Cardiotoxicity.
Frequency/Dose/Duration:	Prescribe at a low dose at night and gradually increase (e.g., amitriptyline 25mg QHS, increase by 25mg each week) until a sub-maximal or maximal dose is achieved, sufficient effects are achieved, or adverse effects occur. Generally, lower doses (e.g., amitriptyline 25 to 75mg a day) to avoid adverse effects and necessity of blood level monitoring, particularly as no evidence of increased pain relief at higher doses. For CRPS, duration may be indefinite, although most patients do not require indefinite treatment as the condition usually improves or resolves spontaneously. Imipramine is less sedating, thus if there is carryover daytime sedation, it may be a better option. If the patient cannot sleep, amitriptyline is recommended as the initial medication to prescribe.
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.
Rationale:	There are no quality studies suggesting efficacy of tricyclic anti-depressants for treatment of CRPS, however there is evidence these agents are effective for treatment of neuropathic pain. Tricyclic antidepressants are not invasive, have adverse effects that range from modest to intolerable, are low cost, have evidence of some efficacy for treatment of neuropathic pain and so are selectively recommended for treatment of CRPS.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for

inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating tricyclic anti-depressants for the treatment of CRPS.

Duloxetine for CRPS

Recommended.

A trial of duloxetine is recommended for treatment of CRPS after attempting other treatments with documented efficacy (e.g., strengthening exercises, aerobic exercise, bisphosphonates) and if TCAs are not tolerated.

Strength of Evidence **– Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	CRPS that is sufficient to require medication. Generally should also have failed multiple other modalities including progressive strengthening exercise, aerobic exercise, NSAIDs, tricyclic anti-depressants, and anti-convulsant agents.
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also has adverse effects including nausea, constipation, dizziness.
Frequency/Dose/Duration:	60mg QD. There appears to be either a minimal or no advantage of the BID dosing over the 60mg QD dosing. Duration for patients with CRPS pain may be as long as indefinitely, although some patients do not require indefinite treatment, particularly if they are compliant with a functional restoration program.
Indications for Discontinuation:	Resolution, development of adverse effects, failure to adhere to a restoration program.
Rationale:	There is no quality evidence of efficacy of duloxetine for treatment of CRPS, however, there is some evidence of efficacy for treatment of peripheral neuropathic pain in comparison with placebo. Duloxetine is not invasive, has low to moderate adverse effects, is moderate cost, has some quality evidence of efficacy for treatment of peripheral neuropathic pain and so, by inference is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is no quality evidence of efficacy of duloxetine for the treatment of CRPS.

Selective Serotonin Reuptake Inhibitors (SSRIs), Bupropion, or Trazodone for CRPS

Not Recommended.

Selective serotonin reuptake inhibitors, bupropion, or trazodone are not recommended for treatment of CRPS without depression. (They may be recommended to treat depression.)

Strength of Evidence – **Not Recommended, Insufficient Evidence**
Level of Confidence – Low

Rationale:	There is no quality evidence selective serotonin reuptake inhibitors, bupropion and trazodone are effective for treatment of CRPS. SSRI antidepressants have evidence of efficacy for treatment of fibromyalgia, otherwise, they have no evidence of efficacy for treatment of other chronic pain conditions (e.g., see Low Back Disorders Guideline). Selective serotonin reuptake inhibitors, bupropion and trazodone are not invasive, have low to modest adverse effects, have no quality evidence of efficacy for treatment of CRPS and no rationale for believing they may be effective, and so are not recommended for treatment of CRPS. They may still be indicated for the treatment of depression, although an SNRI with likely efficacy against CRPS may be a better option.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating selective serotonin reuptake inhibitors for the treatment of CRPS.

Anti-convulsant Agents for CRPS

Recommended.

The use of anti-convulsant agents for treatment of severe CRPS is selectively recommended after attempted management with NSAIDs, other medications with documented efficacy, and a progressive exercise program.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	Generally not indicated, but may be a consideration for severe chronic CRPS as a fourth- or fifth-line agent, and initiated by practitioners familiar with their use and able to monitor patients closely for adverse effects. Treatments that should be attempted first include progressive

	strengthening and aerobic exercises that should be continued. Other prior treatment considerations include other exercises, NSAIDs, bisphosphonates and anti-depressants (TCA and SNRI).
Benefits:	Theoretical potential to improve pain.
Harms:	Caution is warranted for prescribing such agents in patients employed in safety-sensitive positions as such medications cause sedating effects. These medications also may raise concerns about fitness for duty due to the possibility of a seizure disorder. Carbamazepine may cause fluid and electrolyte abnormalities. Topiramate may cause renal stones and ocular toxicity.
Frequency/Dose/Duration:	Frequency and dosing per manufacturer. Duration for CRPS patients may be indefinitely, although most of these patients do not require indefinite treatment as the condition usually improves or resolves spontaneously.
Indications for Discontinuation:	Resolution of pain, lack of efficacy, development of adverse effects.
Rationale:	There are no quality studies evaluating these medications for CRPS. This class of medications has long been thought to be effective for treatment of neuropathic pain (see Neuropathic pain section). However, that may not be correct.[197] There now appears to be no clear pattern to allow a single conclusion of efficacy for these medications for a group of disorders. Instead, treatments appear to require specification or individualization. There is some evidence for efficacy against neuropathic pain and there is quality evidence that topiramate is effective for the treatment of chronic LBP[197] (see Low Back Disorders guideline). The most commonly used anti-convulsant is carbamazepine. However, it has not been studied in large, moderate- or high-quality studies for purposes of treating chronic pain including CRPS. There is evidence suggesting efficacy from an experimental design utilizing carbamazepine for the management of peripheral neuropathic pain.[193] Moderate-quality RCTs conflict regarding whether a related compound, oxcarbazepine, is effective in treating diabetic neuropathy.[196, 347] Thus, it is unclear whether that related compound or even carbamazepine is useful for treating neuropathic pain (or CRPS). This suggests that other options should be attempted first. Lamotrigine has also been studied and has been found to be effective for treating diabetic neuropathy, although the magnitude of benefits is not large.[191, 194] Lamotrigine was not found useful as an adjunct to treatment with other agents such as tricyclic anti-depressants.[192] There is quality evidence that topiramate is not effective for treating painful diabetic neuropathy,[195] although a small quality study showed weak benefits.[198] Dropout rates are high with topiramate (37 to 62%), which suggests that the medication is not well tolerated. Anti-convulsant agents may be reasonable fourth- or fifth-line treatments (e.g., after trials of different NSAIDs, strengthening exercises, aerobic exercise, other exercise, anti-depressants) for CRPS. These drugs are not invasive, have some adverse effects, and may be moderately costly. As they benefit some forms of neuropathic pain, anti-convulsants conceivably could be of benefit for CRPS. These

agents are generally used for neuropathic pain and thus may be reasonable options for CRPS after more efficacious treatment strategies are implemented.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are high and/or moderate-quality RCTs or crossover trials incorporated into this analysis. However, there are no quality studies evaluating anti-convulsant agents for the treatment of CRPS.

Short-term Use of Gabapentin or Pregabalin for CRPS

Recommended.

Short-term use of gabapentin or pregabalin is recommended for treatment of moderate to severe CRPS if other therapies have proven insufficient to control symptoms.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications: CRPS in whom other methods to control symptoms have been proven to be unsuccessful, including strengthening exercises, aerobic exercises, other exercises, NSAIDs, physical therapy/occupational therapy, bisphosphonates, clonidine, and tricyclic anti-depressants. Should be used as an adjunct to a functional restoration program to facilitate the program advancement for the 4 weeks that the medication shows some evidence of efficacy. There is no recommendation for ongoing treatment beyond one course.

Benefits: Improved pain control, may include reduced sleep disturbance. Improved ability to tolerate and engage in progressive exercise program.

Harms: Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also has adverse effects including nausea, vomiting, dizziness.

Frequency/Dose/Duration: One trial utilized gabapentin 600mg QD x 2 days, then 600mg BID x 2 days, then 600mg TID for Days 5 to 21. Duration of use for CRPS patients is usually limited as most of these patients do not require indefinite treatment. The condition usually improves or resolves spontaneously. However, the efficacy of gabapentin has been labeled

	as “mild” for CRPS and quality evidence suggests that benefits are short-term [348].
Indications for Discontinuation:	Resolution, intolerance, adverse effects, or failure to objectively improve during a trial period of medication initiation. Discontinue after 4 weeks unless clearly objective evidence of ongoing, continuing improvement as evidence suggests loss of efficacy with no demonstrable benefits from a second 3-week course.[348]
Rationale:	There is one moderate quality trial suggesting gabapentin is mildly effective for a short-term trial for CRPS [348]. Gabapentin and pregabalin are not invasive, have significant adverse effects in some patients, are low to moderate cost, have evidence of modest efficacy and thus are recommended for a short-term course as an adjunct to more effective treatments.

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	Follow-up:	*Results:*	*Conclusion:*	*Comments:*
van de Vusse 2004 (score = 8.0)		Crossover Trial	Sponsored by Parke-Davis. COI, Parke-Davis supplied gabapentin and matching placebo capsules for this trial. Drs. Van de Vusse and Weber have received financial support from Parke-Davis	N = 58 with CRPS I in affected limb	Mean age: 44 Sex(M:F) 11:48	Gabapentin 600mg once a day for Day 1-2, then 600mg BID Day 3-4, then 600mg TID. Day 5-21 vs. placebo for 3 weeks each, separated by 2-week washout period.	3,5,8 weeks	Symptom durations averaged 43 to 44 months. Intervention group received gabapentin, followed by washout period and placebo treatment. Control received placebo treatment, followed by washout period and gabapentin treatment. Both gabapentin and identical placebo capsules delivered immediately before start of 2-medication period. Global perceived effect showed more improvement in gabapentin (43% vs. placebo 17%). However, no benefit in second 3-week course of treatment.	"Patients reported significant pain relief in favor of gabapentin in the first period. Therapy effect in the second period was less; finally resulting in no significant effect combining results of both periods. The CRPS patients had sensory deficits at baseline. We found that this sensory deficit was significantly reversed in gabapentin users in comparison to placebo users."	Blinding questionable due to adverse events. Patients were CRPS I both upper and lower extremity. Adverse events were significantly greater with the use of Neurontin. Only numbness affected significantly by Neurontin, not pain or ROM

Bisphosphonates for CRPS

Strongly Recommended.

Bisphosphonates are strongly recommended for patients with CRPS after physical therapy interventions have been trialed.

Strength of Evidence – **Strongly Recommended, Evidence (A)**
Level of Confidence – High

Indications:	Moderate or severe CRPS, including in acute to subacute as well as chronic phases. Should be included as part of functional restoration plan where strengthening, aerobic and other functional exercises are central foci of prescriptions. However, based on evidence of efficacy, bisphosphonates are one of the earlier medications to be trialed for CRPS.
Benefits:	Improved pain control and ability to tolerate increased exercise regimen.
Harms:	Esophagitis, hyopcalcemia, diarrhea, constipation, bone pain, fatigue, renal insufficiency, jaw osteonecrosis.
Frequency/Dose/Duration:	Taken in oral or parenteral formulations. Treatments used in the quality trials included: Alendronate 40mg QD for 8 weeks; Clodronate 300mg IV QD for 10 days; Alendronate 7.5mg IV QD for 3 days; Pamidronate 60mg IV for one dose; Neridronate 100-mg IV Q 10 days for 40 days. Duration for oral treatment of CRPS patients may be indefinite, although most do not require indefinite treatment as the condition usually gradually improves or in some cases resolves spontaneously.
Indications for Discontinuation:	Resolution, adverse effects, intolerance.
Rationale:	There are high- and moderate-quality studies of bisphosphonates for CRPS. These studies show consistent, generally substantial benefits.[349-353] Patients with either early or established CRPS have been shown to respond favorably to bisphosphonates. Bisphosphonates are either not invasive in oral formulations or are minimally invasive in parenteral administrations, have adverse effects, are moderate to high cost, have evidence of significant efficacy, and are thus recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are high- and moderate-quality RCTs or crossover trials incorporated into this analysis.

Evidence for the Use of Bisphosphonates

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Manicourt 2004 (score = 8.0)		RCT	Supported by Merck Sharpe and Dolme. No mention of COI.	N = 40 with post-traumatic CRPS Type I of lower extremity meeting Harden diagnostic criteria for 7 to 8 months; sprain/strain injuries, surgery, fracture, and contusion; excluded recent inefficacious calcitonin therapy	Mean age: Alendronate group: 44.6±12.3 Placebo group: 45.2±12.5 Sex(M:F) 19:21	Alendronate 40mg a day (n = 20) vs. placebo (n = 20) for 8 weeks.	8 weeks	Alendronate group had significant improvement within 4 weeks vs. placebo. Was a subsequent open trial; those previously on placebo also experienced similar, significant improvements on active medication. At Week 12, significant reduction in mean VAS score in placebo group, p <0.05. Alendronate group saw reductions in mean VAS scores at Weeks 4, 8, and 12 (p <0.05), and sharp increase in mean pressure tolerance score at Week 4, p <0.05. Mean joint mobility score significantly better in treatment group vs. placebo throughout study, p <0.05.	"Our findings support the use of oral alendronate in posttraumatic CRPS I. By reducing local acceleration of bone remodeling, alendronate might relieve pain by effects on nociceptive primary afferents in bone, pain-associated changes in the spinal cord, and possibly also through a central mechanism."	Small numbers. CRPS I of lower extremity appears to benefit from high dose alendronate therapy for up to 16 weeks.
Varenna 2000 (score = 8.0)		RCT	No mention of Sponsorship or COI.	N = 32 recruited with RSDS by Kozin's criteria	Mean Age: 55.6±8.6 Sex(M:F) 13:19	Clodronate 300mg IV QD (n = 15) over 3 hours vs. saline solution (n = 17) for 10 days.	40, 90, 180 days	RSD causes: 28.1% sprain/trauma, 28.1% unknown, 25% fracture, 12.5% post-op/post-arthroscopy, 1 each post acute gouty arthritis and diabetes. VAS (time	"A 10 day IV clodronate course is better than placebo and effective in the treatment of RSDS. Urinary excretion of NTx (N-	Study suggests 10 day IV clodronate provided benefit for CRPS outcomes of clinical pain global

								0/time 40): clodronate (58.4±23.1/22.3±20.2) vs. placebo (62.5±29.0/56.4±31.4), p ≤0.001 at T40. Clinical global assessment: (2.3±0.6/0.9±0.6) vs. 2.2±0.6/1.9±0.7), p ≤0.001 at T40.	telopeptide), a marker of bone resorption, seemed to be a predictive factor for clodronate efficacy."	assessment in this select population, which mostly included post traumatic musculoskeletal injuries, although sample size small.
Adami 1997 (score = 5.5)		RCT	No mention of Sponsorship or COI.	N = 20 with RSDS of foot and hand; apparently met Kozin's criteria; duration 5 to 34 weeks	No mention of mean age: Age Range: Alendronate group: 39-79 Placebo group: 48-80 Sex(M:F) 12:8	Alendronate 7.5mg IV daily (n = 10) for 3 days vs. saline (n = 10).	4 weeks	All but 1 improved on alendronate vs. 3/20 improving on placebo. All on placebo improved in subsequent open-label phase. Pooling RCT and open phases, 5 patients improved at least 75%, and another 8 improved at least 50%.	"[B]isphosphonates should be considered for the treatment of RSDS, producing consistent and rapid remission of the disease."	No mention of co-interventions; small numbers. No differentiation between CRPS I or II. Bisphosphonates appear to help in CRPS.
Robinson 2004 (score = 5.0)		RCT	No mention of Sponsorship or COI.	N = 27 with CRPS who met IASP diagnostic criteria; duration 3 months to 6 years	Mean age: 45 Sex (M:F) 9:18	One dose of pamidronate 60mg IV 9n = 14) vs. saline (n = 13).	1 & 3 months	Pain scores lower in pamidronate group vs. placebo at 3 months (p = 0.043), as were functional scores (p = 0.047).	"Pamidronate may be a useful treatment option in the management of patients with CRPS Type I. Although treatment response was variable, the majority of patients improved. Early administration in tandem with other treatment	Small numbers. Treatment response was variable showing a subset of patients may benefit more than others i.e. upper vs. lower extremity CRPS I patients. No mention of physical activity level or PT during study. Baseline pain was greater in

									measures is recommended."	treatment group.
Varenna 2012 (6.0)	Chronic, CRPS	RCT	The authors declare no conflict of interest.	N = 82 participants with either foot or hand CRPS.	Mean age 57.6, 29 males, 53 females.	Both groups received four 100-mg infusions over 10 days for 40 days. The control group (N = 41) received an intravenous placebo, with the comparison group (N = 41) receiving neridronate.	Outcome assessments were taken previous to randomization and prior to the first day of treatment, then follow-ups at day 10, 20 and 40 days of treatment. 10 days after the study, the placebo group received the neridronate treatment with a follow-up performed at day 40.	At day 20 of treatment, statistically significant results were see in the neridronate group in a decreased visual analogue (VAS, measures pain) score (P=0.043).	"In patients with acute CRPS-I, four i.v. infusions of neridronate 100mg are associated with clinically relevant and persistent benefits. These results provide conclusive evidence that the use of bisphosphonate, at appropriate doses, is the treatment of choice for CRPS-I."	Meaningful improvements in pain, function, emotional well being, physical and mental components of outcome assessments, favoring neridronate treatment. (Medication not approved for use in USA).

Calcitonin for CRPS

Recommended.

Calcitonin is recommended as a treatment option for CRPS patients.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications:	Severe CRPS with inadequate symptom relief with strengthening, aerobic exercise, NSAIDs, corticosteroids, active physical and/or occupational therapy, and bisphosphonates.
Benefits:	Improved pain control and ability to tolerate progressive exercises.
Harms:	Muscle cramps, fever, chills, dizziness, joint pain, nausea, vomiting, seizures.
Frequency/Dose/Duration:	Dosing in the quality trials were intranasal calcitonin: 100IU TID for 3 weeks [354], 400IU QD for 4 weeks [355], and 200 IU QD plus calcium 500mg a day [356]. Duration of use for CRPS patients may be indefinite, although most do not require this as the condition usually improves or resolves spontaneously.
Indications for Discontinuation:	Recovery, intolerance, adverse effects, failure to improve, reaching the end of a 2-month period without objective evidence of ongoing improvement.
Rationale:	There are a few heterogeneous studies on the efficacy of calcitonin for CRPS. The studies do not agree, as some indicate a benefit [340, 354, 357] and some do not[355, 356]. There is no clear pattern elucidated from the studies rated as higher quality. Due to data heterogeneity, it is questionable to combine these data in a meta-analysis. Both studies using parenteral calcitonin were positive,[340, 357] possibly indicating a problem with dose and route of administration. The literature in this area also conflicts significantly about the ideal timing of administration. One guideline recommends calcitonin for significant osteopenia, immobility, and trophic changes,[128] while others used it early in the disease process.[354] This literature contrasts with that for bisphosphonates, which have much better evidence for efficacy. Calcitonin is minimally invasive, has relatively few adverse effects, and is moderately costly. The mechanism of action in CRPS is unknown. Calcitonin is recommended for patients who do not have adequate symptom relief with NSAIDs, corticosteroids, and physical/ occupational therapy or for those with a contraindication for a bisphosphonate.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from

Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are moderate-quality RCTs incorporated into this analysis. There are 2 low-quality RCTs in Appendix 4.

Evidence for the Use of Calcitonin

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Bickerstaff 1991 (score = 7.0)		RCT	Supported by Sandoz Pharmaceuticals PLC, and an MRC Programme Grant. No mention of COI.	N = 40 with chronic reflex sympathetic dystrophy (algodystrophy) screened 2 weeks after cast removal for Colles' fracture with diagnoses made based on pain/tenderness, vascular instability, swelling and stiffness	Mean age: Calcitonin group: 60.8 ± 1.8 Placebo group: 65.5±1.8 Sex(M:F) 6:34	Nasal calcitonin 400IU daily (n = 20) vs. normal saline (n = 20) for 4 weeks.	12 weeks	No statistically significant results for any major outcomes such as pain, vascular instability, dolorimetry, hand swelling or grip strength, all of which improved over time in both groups. Graphs suggest trends in favor of placebo over calcitonin; however, dolorimetry and stiffness favored calcitonin.	"Although this study demonstrates a rapid effect of calcitonin [sic], it also confirms that spontaneous resolution of symptoms occurs commonly in algodystrophy. Consequently, open studies evaluating the use of calcitonin should be interpreted with caution" as "no demonstrable effect on the clinical or skeletal progression of the disorder using sensitive methods of measuring the response to treatment" was found.	Study negative. Authors questioned whether amount of calcitonin in nasal inhalation formulation had been sufficient.

Gobelet 1992 (score = 6.5)		RCT	No mention of sponsorship or COI.	N = 66 with post-traumatic reflex sympathetic dystrophy (8 to 10 weeks duration) eligible fulfilled Kozin's criteria, Steinbrocker's stage	Mean age: Group 1: 50.2±16.7 Group 2: 49.8±12.3 Sex(M:F) 41:25	Physical therapy and 100 units TID of salmon calcitonin intranasally (n = 35) vs. physical therapy and placebo (n = 35) for 3 weeks.	60 days	Statistically significant differences between groups in pain on motion end of 1st week (p <0.005) and persisting thru 2 months (p <0.04). Pain at rest significant for calcitonin at Weeks 3 (p <0.02) and 8 (p <0.007). ROM improved in calcitonin Weeks 1 (p <0.04) and 8 (p <0.04). NS for edema.	"[S]almon calcitonin has an effect but that this effect was not equally observed on all parameters analyzed. It was most marked on pain (at rest and on movement) and on the ability to work."	No mention of co-interventions. No differentiation between CRPS I or II. Data suggest modest efficacy.
Sahin 2006 (score = 5.0)		RCT	No mention of sponsorship or COI.	N = 35 with CRPS Type I, Stage I, after fractures in Turkey; Steinbrocker criteria used for ascertaining Stage I	Mean ageL Paracetamol group: 60.0±12.32 Calcitonin Group: 57.72±12.33 Sex(M:F) 10:25	Intranasal salmon calcitonin (200 IU a day plus calcium 500mg a day) (n = 18) vs. paracetamol (1,500mg a day) (n = 17) for 2 months.	3 weeks	Mean durations of symptoms: 5.4 and 6.0 weeks with trauma 12.7 weeks previously; casting in all 1st 5.5-5.8 weeks after trauma. PT 5 times a week for 3 weeks. PT included "stellate ganglion blockage with ultrasound," TENS to affected hand (20 minutes), contrast bathing, and ROM exercises. VAS scores (baseline/2 months): paracetamol 6.12±1.5 to 3.12±1.8 vs. calcitonin 5.83±1.54 to 2.22±1.93. Other ROM and temperature favored calcitonin, but not significant between groups.	"[C]alcitonin does not make any favourable contribution in the treatment of patients with acute CRPS I; physical therapy combined with only a simple analgesic is an efficient means of therapy."	Data suggest that calcitonin has weak effect over that of paracetamol, but study not powered to detect that effect.

Clonidine for CRPS

Recommended.

Clonidine administered by oral or regional blockade is recommended for treatment of moderately severe CRPS that is not responsive to rehabilitative therapy, NSAIDs, or glucocorticosteroids.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications:	Severe CRPS that is not responsive to strengthening exercises, aerobic exercise, other exercise, NSAIDs, bisphosphonates, and glucocorticosteroids.
Benefits:	Improved pain control and ability to progress with functional exercises
Harms:	Adverse effects related to either clonidine, lidocaine and/or NSAID. Includes hypotension, dysrhythmias.
Frequency/Dose/Duration:	Three injections at weekly intervals. The single quality study used: 30µg clonidine plus 1mg/kg lidocaine plus 0.9% saline solution plus 5mg parecoxib [342]. As parecoxib is not available in the US, other NSAIDs should be considered.
Indications for Discontinuation:	Resolution, intolerance, adverse effects, failure to improve. For IV administrations, reaching the end of the series of 3 injections.
Rationale:	There is one moderate quality trial suggesting that an intravenous regional blockade that includes clonidine, parecoxib and lidocaine is superior to placebo [342]. Intravenous regional blockades are invasive, have adverse effects, are moderate to high cost, have some evidence of efficacy and thus are selectively recommended. However, while there are no direct comparative studies, overall results suggest the magnitude of benefits may be greater for bisphosphonates, thus some physicians may opt to use them preferentially before resorting to clonidine if needed. There are no quality studies of oral clonidine treatment, but efficacy is suggested by the results from interventional routes of administration.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are moderate-quality RCTs or crossover trials incorporated into this analysis.

Evidence for the Use of Clonidine

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Rauck 1993 (score = 5.0)		RCT, Crossover trial	No mention of Sponsorship or COI.	N = 26 with RSD	Mean age: 38±1.8 No mention of sex.	Normal saline vs. 300µg clonidine vs. 700µg clonidine with follow-ups at 20, 40 60, 120, 180, 240 and 360 minutes after injection.	6 hours	McGill scores decreased with placebo from 36.0 to 35.7; in 300µg from 38.0 to 29.9; and 700µg dose from 37.2 to 25.7.	"[E]xtensive analgesia may be obtained by epidural administration. Sedation and hypotension may limit bolus epidural clonidine administration for RSD. The role for chronic epidural infusion of clonidine has not been established."	Blinding not well described; no long-term results reported despite continued treatment offered. Longer term infection complication rate of 31.6% (1 case of meningitis) over 40 days treatment is concerning.
Frade 2005 (score = 5.5)		RCT	No mention of Sponsorship or COI.	N = 30 with CRPS Type I in upper limb	Mean age: CG group 41, IVRAPG group 41, SPG group: 44. Sex(M:F) 13:17	30µg clonidine plus 1mg/kg lidocaine plus 0.9% physiologic solution (control, CG, n = 10) vs. 30µg clonidine plus 1mg/kg lidocaine plus 0.9% physiologic solution plus 5mg parecoxib (group IVRAPG, n = 10) v. 30µg clonidine plus 1mg/kg lidocaine plus 0.9% physiologic solution (SPG, n = 10) 3 times at weekly intervals.	3 weeks	VAS before/60 minutes after each intervention: CG Week 1 (8±1.15/2.6±1.9), Week 2 (5.9±1.1/1.5±0.97), Week 3 (5±1.66/2.1±1.97); IVRAPG Week 1 (8±1.56/2.4±2.67), Week 2 (5.8±2.4/1.2±1.98), Week 3 (3.1±1.66/0.6±1.26); SPG Week 1 (8.3±1.25/2.6±3.1), Week 2 (6±1.83/1.5±1.08), Week 3 (5±1.56/2.2±1.8), CG vs. SPG decrease Week 1 to 2. Mean daily oral ketoprofen consumption end of each week (1st/2nd/3rd week): CG (180±92/150±97/170±106) vs. IVRAPG (170±106/60±70/70±80) vs. SPG (190±74/150±108/160±96), IVRAPG smaller consumption 2nd and 3rd week vs. other groups, p <0.05.	"[I]n contrast to IV systemic 20 mg of parecoxib, IV 5 mg of parecoxib was an effective coadjuvant combined with weekly clonidine/lidocaine loco-regional block for CRPS type 1."	Data suggest parecoxib may have additive benefit when combined with clonidine.

Intravenous Regional Anesthesia with Clonidine for Preventive Administration Prior to Surgery

Moderately Recommended.

Intravenous regional anesthesia with clonidine is recommended for administration prior to surgery to prevent recurrence of CRPS in patients who have previously had CRPS. It may also be considered in patients undergoing surgery who are considered at increased risk for CRPS.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications:	Patients undergoing surgery who have a prior history of CRPS. May be considered for those at high risk for CRPS.
Benefits:	Potential prevention of CRPS
Harms:	Hypotension, dysrhythmias.
Frequency/Dose/Duration:	IV administration
Indications for Discontinuation:	Adverse effects, completion of a block.
Rationale:	One moderate quality study has suggested efficacy of intravenous clonidine for preventing CRPS recurrence in a peri-operative timeframe[206]. Epidural administration of clonidine is invasive, has adverse effects, is moderate cost, has demonstrable efficacy for prevention of recurrence of CRPS and is thus selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 moderate-quality RCT and 1 moderate-quality crossover trial incorporated into this analysis.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size/Population:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Reuben 2004 (score = 7.5)		RCT	No mention of sponsorship or COI.	N = 84 with history of upper extremity CRPS undergoing surgery on affected extremity	Mean age: IVRA-L group: 47±11 IVRA-C: 52±14 Sex(M:F) 17:67	Intravenous regional anesthesia with 0.5% lidocaine (IVRA-L) 1mL NS added to IVRA solution (n = 42) vs. intravenous regional anesthesia with clonidine 1µg/kg (IVRA-C) (n = 42).	1 year	Recurrence rate of CRPS significantly lower in patients receiving IVRA with lidocaine and clonidine vs. IVRA lidocaine only, p <0.001.	"Intraoperative IVRA with lidocaine and clonidine on patients with a history of CRPS can significantly reduce the recurrence rate of this disease process."	No differentiation between CRPS I or II. No mention of co-interventions during follow-up period.

Oral Glucocorticosteroids for CRPS

Recommended.

Glucocorticosteroids are recommended for short-term treatment of CRPS.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications:	Moderate to severe CRPS with symptoms insufficiently controlled with progressive strengthening, aerobic and other active exercises, and NSAIDs. Bisphosphonates are another reasonable option at this stage. Few patients with mild CRPS may be candidates, especially if there is a lack of progress or worsening of symptoms.
Benefits:	Improved pain and improved function with better tolerance of exercises.
Harms:	Agitation, worsening diabetes or glucose intolerance, weight gain, hypertension or worsened blood pressure control, infection. Generally relatively limited for a short-term treatment such as for CRPS; while longer term treatment has significantly greater adverse effects.
Frequency/Dose/Duration:	One regimen used was Prednisolone 40mg PO QD for 14 days and then 10 mg/week taper [341]. A second regimen was prednisone 10mg PO TID for up to 12 weeks [300]. There is no comparative evidence to suggest which regimen is superior. If there is significant improvement in objective findings and an additional treatment is felt to be indicated, it appears reasonable to continue treatment for an additional two months. Subsequent treatment should be individualized based on ongoing improvements, and inadequacy of progressive exercises.
Indications for Discontinuation:	Completion of a course of treatment, sufficient clinical response to provide for progressive exercise program compliance, non-tolerance or adverse effects.
Rationale:	Oral glucocorticosteroids to treat CRPS have been assessed in three small-scale studies, two of which have significantly positive effects suggesting meaningful benefits.[300, 341] Oral glucocorticosteroids are not invasive, have adverse effects, are low cost, have evidence of efficacy and are thus recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 2 moderate-quality RCTs incorporated into this analysis.

Evidence for the Use of Oral Glucocorticosteroids

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Kalita 2006 (score = 6.0)		RCT	No mention of sponsorship or COI.	N = 60 with CRPS I following stroke diagnosed with a severity scale	Mean age: 56 Sex (M:F) 40:20	Prednisolone 40mg daily for 14 days and then 10 mg/ week taper (n = 30) vs. piroxicam 20mg daily (n = 30) for 1 month.	1 month	All measures improved in prednisolone; only autonomic improved in piroxicam group. Improvement observed in symptoms and signs of CRPS I following stroke in 83.3% in prednisolone group and 16.7% in piroxicam. CRPS total score (prednisolone vs. piroxicam): 19.07 vs. 41.93, p <0.0001.	"Prednisolone resulted in significant improvement in the symptoms and signs of CRPS I following stroke, compared to piroxicam. Both drugs produced an improvement in the BI [Barthel index] score."	Data suggest steroid effective.
Christensen 1982 (score = 4.0)		RCT	No mention of sponsorship or COI.	N = 23 with RDS due to Colles', humeral, olecranon, or other fracture, sequela of abscess incision	Mean age: 66 Sex (M:F) 3:20	Oral prednisone 10 mg TID (n = 13) vs. placebo (n = 10) for up to 12 weeks.	12 weeks	All 13 patients on prednisone improved at least 75% vs. 2 of 10 (20%) in the placebo.	"Prednisone appears superior to other treatment in RSD, although the mode of action is not known."	Inter-group difference statistically significant in favor of steroid.

Intrathecal Glucocorticosteroids for CRPS

Not Recommended.

Intrathecal glucocorticosteroids are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – Low

Rationale:	Oral glucocorticosteroids to treat CRPS have evidence of efficacy [300, 341]. However, a moderate quality study of intrathecal administration of methylprednisolone [358] has evidence of a lack of efficacy. Intrathecal glucocorticosteroids are invasive, have adverse effects, are moderate to high cost, have evidence of a lack of efficacy and are thus not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is one moderate-quality RCTs incorporated into this analysis.

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Munts, 2010 (score=5.0)	CRPS	RCT	Sponsored by Dutch government grant (BSIK03016) and no COI.	N=21 patients	Mean age: 46±11 years; 5 males, 16 females.	Methylprednisolone group: single intrathecal administration of 60 mg methylprednisolone acetate vs Placebo group: 1.5 mL sodium chloride	12 weeks	Study was ended prematurely due to lack of reaching efficacy. No significant difference between groups was observed at 6 weeks (t=.65, d.f.=18, p=.53, difference in means 0.3, 95% CI -.7-1.3). Myoclonus deteriorated in ITM group while not in the placebo group which led to a significant difference (F(1,17=6.17, p=.02, partial eta squared=.27). No significant difference between groups was observed in any other outcome measures. No serious AE's occurred; however, 8 patients experienced headaches, 9 patients had backaches.	"(A) single bolus administration of ITM is not efficacious in chronic CRPS patients, which may indicate that spinal immune activation does not play an important role in this phase of the syndrome."	Possible randomization failure and small sample size. All participants were referred to the movement disorder outpatient clinic, may not be generalizable.

Ketamine Infusion for CRPS

Not Recommended.

Ketamine infusion is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies on efficacy of ketamine for CRPS. One low quality study suggested lack of efficacy at 12 weeks [359]. Ketamine is invasive, has adverse effects (e.g., respiratory depression and hallucinations), is moderately costly, has no quality evidence of efficacy and thus is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating ketamine for the treatment of CRPS. There is 1 low-quality RCT in Appendix 4.

Ketanserin for CRPS

No Recommendation.

There is no recommendation for or against the use of ketanserin for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies reported evaluating ketanserin to treat CRPS. Thus, there is no recommendation for or against its use to treat CRPS.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from

other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating ketanserin for the treatment of CRPS or other chronic pain conditions. There is 1 low-quality RCT in Appendix 4.[210]

Magnesium Sulfate for CRPS

Not Recommended.

Magnesium sulfate is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – Low

Rationale: There is one moderate quality study evaluating magnesium sulfate to treat CRPS [360]. This study found no meaningful differences between groups for any outcomes at 12 weeks. Magnesium sulfate is invasive, has some adverse effects, is low to moderate cost, but has quality evidence of a lack of efficacy and is thus not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria.There is one moderate quality studies evaluating magnesium sulfate for the treatment of CRPS or other chronic pain conditions. There is one low quality RTC in Appendix 4.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Fischer 2013 (4.0)	CRPS	RCT	No COI. Supported by TREND via a government grant from The Netherlands.	N = 56 with CRPS-I (according to IASP Orlando critiera)	52 female, 4 male. Mean age 46.7 years	70mg/kg of magnesium sulphate (N = 29) vs placebo (NaCL 0.9%) (N = 27); both treatment given through intravenous infusion of 25mL/h for 4 hours a day for 5 days	12 weeks	Pain scores (numeric rating scale) at baseline, T1-T4: Placebo - 6.3, 5.4, 5.5, 5.3, 5.4, $MgSO_4$ – 6.1, 5.2, 5.3, 5.2, 5.1. No significant differences between groups in BOX-11 and ISS scores (P>0.05).	"Administration of the physiological competitive N-methyl-D-aspartate receptor antagonist magnesium in chronic CRPS provides insufficient benefit over placebo. Future research should focus on patients with acute CRPS and early signs and symptoms of central sensitization."	No meaningful differences between groups for any outcomes assessed at 12 weeks.

NMDA Receptor/Antagonists

Not Recommended.

NMDA receptor/antagonists, including dextromethorphan, are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality studies evaluating NMDA receptor/antagonists other than dextromethorphan for treatment of chronic pain [207-209] and no quality evidence for treatment of CRPS. NMDA receptor/antagonists are not invasive, have some adverse effects, are low cost, but in the absence of quality evidence of efficacy, these agents are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating NMDA receptor/antagonists for the treatment of CRPS.

Muscle Relaxants for CRPS

No Recommendation.

There is no recommendation for or against the use of muscle relaxants for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There is no quality evidence of efficacy of skeletal muscle relaxants for treatment of CRPS. Skeletal muscle relaxants are not invasive, have moderate adverse effects, are low cost, have no quality evidence of efficacy for treatment of CRPS and are thus not recommended. However, there are other indications for use of these agents that may also occur in CRPS patients (e.g., see Low Back Disorders Guideline).

Regardless, Diazepam appears to be inferior to other skeletal muscle relaxants,[212, 217] has a higher incidence rate of adverse effects, and is addictive. **Therefore, diazepam is not recommended for use as a skeletal muscle relaxant.** Evidence suggests that carisoprodol is

comparable to cyclobenzaprine but is not indicated for reasons of abuse potential. Chlorzoxazone has been associated with hepatocellular toxicity. Chlormezanone has been implicated in Stevens-Johnson syndrome and toxic epidermal necrolysis.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are high- and moderate-quality RCTs incorporated into this analysis. There are no quality studies evaluating skeletal muscle relaxants for the treatment of CRPS. There are 2 low-quality RCTs,[218, 219] in Appendix 4.

Thalidomide and Lenalidomide for CRPS

Not Recommended.

Thalidomide is not recommended for the treatment of CRPS or any other chronic pain syndrome.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – Low

Rationale: A moderate quality trial found lack of efficacy of lenalidomide for treatment of CRPS [361]. Lenalidomide has fewer adverse effects than thalidomide. Regardless, these medications are not invasive, have modest to high adverse effects, have no evidence of efficacy and thus are not recommended for treatment of CRPS.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is one moderate-quality RCTs incorporated into this analysis.

Evidence for The Use of Lenalidomide

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Manning 2014 (6.5)	Lenalidomide	RCT	Supported by Celgene Corporation. Manning was an employee of Celgene Corporation during trial period as well as Alexander and Arezzo.	N = 180 CRPS type 1 (via Budapest research criteria) for ≥1 year with unilateral or bilateral involvement of a distal hand or foot, with or without proximal spread, plus CRPS-related pain intensity score of ≥4 in index limb	144 female, 36 male. Mean age 44.5 years	Lenalidomide, 10 mg orally once daily (N = 68) vs Placebo (N = 79)	12 weeks post first treatment, possibility to continue to extension phase for 4 additional weeks	CRPS PI-NRS (Pain Intensity Ratings) Scores: Lenalidomide AM+PM time combined score - Baseline 7.1±1.4, Week 12 6.5±2.1, change -.7±1.7. AM scores - Baseline 6.9±1.5, Week 12 6.3±2.1, change -.6±1.7. PM scores - Baseline 7.3±1.4, Week 12 6.6±2.1, change -.7±1.7. Placebo AM+PM time combined score - Baseline 7.0±1.6, Week 12 6.6±2.3, change -.4±1.5. AM scores - Baseline 6.9±1.7, Week 12 6.5±2.3, change -.3±1.5. PM scores - Baseline 7.1±1.6, Week 12 6.7±2.3, change -.4±1.5. No significant differences in pain scores (AM+ PM (P=.26), AM (P=.28), PM (P=.27))	"In summary, because the current study found no evidence of efficacy of lenalidomide in the sample studied, despite its relative safety, it cannot be endorsed for the broad population of people with CRPS. Given that failure rates are high in parallel-group, placebo controlled trials of pain therapies, it may be reasonable to consider additional study of lenalidomide in specific subgroups of patients."	High dropout rate due to adverse events. No meaningful differences between groups.

Capsicum Creams for CRPS

No Recommendation.

There is no recommendation for or against the use of capsicum creams for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There is no quality evidence of efficacy of capsicum for treatment of CRPS. Capsicum is not invasive, has modest adverse effects, is low to moderate cost in aggregate, has no evidence of efficacy for treatment of CRPS and thus there is no recommendation.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria.

DMSO for CRPS

Recommended.

DMSO is recommended for treatment of CRPS.

Strength of Evidence – Recommended, Insufficient Evidence (I)
Level of Confidence – Low

Indications:	CRPS that is sufficient to require medication. Generally should also have failed multiple other modalities including progressive strengthening exercise, aerobic exercise, NSAIDs, tricyclic anti-depressants, bisphosphonates, and anti-convulsant agents.
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	May have dermatological effects, dry skin, breathing difficulties, garlic taste, headache, dizziness, drowsiness, diarrhea, constipation.
Frequency/Dose/Duration:	DMSO applied 50% 5 times a day to affected extremity. Duration in the highest quality study was 17 weeks [362]. Some patients do not require lengthy treatment, particularly if they are compliant with a functional restoration program which should be the key focus of the treatment program.

Indications for Discontinuation:	Resolution, development of adverse effects, failure to adhere to a restoration program.
Rationale:	There is one low quality, placebo-controlled study suggesting some modest efficacy of DMSO. One high-quality trial had no placebo control and found comparable efficacy with N-Acetylcysteine [362]. Adverse effects (skin reactions) occur in approximately 4% of patients.[362] Although two studies suggest benefit, flaws in their design preclude drawing robust conclusions regarding DMSO's efficacy. DMSO is not invasive, has generally low adverse effects, is moderately costly in aggregate, has some evidence suggesting efficacy and thus it is selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is one high-quality RCT incorporated into this analysis. There is one low quality RTCs in Appendix 4.

Author Year (Score):	Category	Study type:	Conflict of Interest	Sample size:	Age/Sex	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Perez 2003 (score = 8.0)	DMSO, NAC, EMLA	RCT	Study supported by Dutch National Health Council. No mention of COI.	N = 145 with CRPS I affected limb (i.e., upper or lower) who met Veldman criteria and durations since trauma 86-102 days	49 males, 96 females; Mean age DMSO: 50.08±13.28, NAC: 48.94±15.39.	Intervention Group 1 received 50% DMSO 5 times a day to affected extremity (n = 71) vs. Intervention Group 2 received NAC 600mg effervescent tablets 3 times a day (n = 74). Both intervention groups received dummy placebos for 17 weeks.	Baseline, 6, 17, 32, 52 weeks.	At 52 weeks, CRPS-I treated with DMSO improved more than NAC. CRPS I-cold improved more with NAC than DMSO. Significant differences for subscores of lower extremity function favored DMSO. Subgroup analysis more favorable DMSO for warm CRPS I; NAC significantly better for cold. Results negatively influenced if duration of complaint longer. Treatment with DMSO and NAC equally effective in treating CRPS I. Strong indications for differences in effects of subgroups with warm or cold CRPS I: warm CRPS I, DMSO-treatment appeared more favorable, while for cold CRPS I, NAC-treatment appeared more effective.	"[B]oth DMSO 50% and N-acetylcysteine are equally effective in treatment of CRPS I. Treatment for cold CRPS I with DMSO 50% seems unadvisable , and N-acetylcysteine would be the preferred treatment."	Lack of a placebo limits conclusions on treatment efficacy. One interpretation that cannot be eliminated is that both treatments may be equally ineffective. Another conclusion could be substantial difference in paracetamol use between groups; it masked potentially greater efficacy in DMSO group, although tramadol use higher in DMSO. Results for stratification by cold vs. warm CRPS more impressive, suggest possible meaningful differences.

N-Acetylcysteine (NAC) for CRPS

Recommended.

NAC is recommended for treatment of CRPS as an adjunct to an active therapy and exercise program.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	CRPS that is sufficient to require medication. Generally should also have failed multiple other modalities including progressive strengthening exercise, aerobic exercise, NSAIDs, tricyclic anti-depressants, bisphosphonates, and anti-convulsant agents.
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	GI adverse effects often sufficient to require discontinuation.
Frequency/Dose/Duration:	N-Acetylcysteine 600mg PO TID. Duration in the quality trial was 17 weeks [362]. Some patients do not require lengthy treatment, particularly if they are compliant with a functional restoration program which should be the key focus of the treatment program.
Indications for Discontinuation:	Resolution, intolerance, development of adverse effects, failure to respond.
Rationale:	NAC has evidence of comparative efficacy with DMSO (Perez 03), but no quality placebo-controlled evidence of efficacy. NAC is not invasive, but has severe GI adverse effects resulting in discontinuation of treatment in 6.8% of patients,[362] is moderately costly in aggregate, has evidence somewhat suggestive of efficacy and thus NACis recommended for treatment of CRPS.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is one high-quality RCT incorporated into this analysis.

Evidence for the Use of Dimethyl sulfoxide, N-Acetylcysteine, and EMLA Cream

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Perez 2003 (score = 8.0)	DMSO, NAC, EMLA	RCT	Study supported by Dutch National Health Council. No mention of COI.	N = 145 with CRPS I affected limb (i.e., upper or lower) who met Veldman criteria and durations since trauma 86-102 days	49 males, 96 females; Mean age DMSO: 50.08±13.28, NAC: 48.94±15.39.	Intervention Group 1 received 50% DMSO 5 times a day to affected extremity (n = 71) vs. Intervention Group 2 received NAC 600mg effervescent tablets 3 times a day (n = 74). Both intervention groups received dummy placebos for 17 weeks.	Baseline, 6, 17, 32, 52 weeks.	At 52 weeks, CRPS-I treated with DMSO improved more than NAC. CRPS I-cold improved more with NAC than DMSO. Significant differences for subscores of lower extremity function favored DMSO. Subgroup analysis more favorable DMSO for warm CRPS I; NAC significantly better for cold. Results negatively influenced if duration of complaint longer. Treatment with DMSO and NAC equally effective in treating CRPS I. Strong indications for differences in effects of subgroups with warm or cold CRPS I: warm CRPS I, DMSO-treatment appeared more favorable, while for cold CRPS I, NAC-treatment appeared more effective.	"[B]oth DMSO 50% and N-acetylcysteine are equally effective in treatment of CRPS I. Treatment for cold CRPS I with DMSO 50% seems unadvisable , and N-acetylcysteine would be the preferred treatment."	Lack of a placebo limits conclusions on treatment efficacy. One interpretation that cannot be eliminated is that both treatments may be equally ineffective. Another conclusion could be substantial difference in paracetamol use between groups; it masked potentially greater efficacy in DMSO group, although tramadol use higher in DMSO. Results for stratification by cold vs. warm CRPS more impressive, suggest possible meaningful differences.

EMLA Cream for CRPS

No Recommendation.

There is no recommendation for or against the use of EMLA cream for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: EMLA cream has no quality studies supporting its efficacy. EMLA is not invasive, has low adverse effects, is moderately costly in aggregate, but in the absence of efficacy there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating EMLA cream for the treatment of CRPS. There is 1 high-quality RCT incorporated into this analysis. There is 1 low-quality RCT [220] in Appendix 4.

Tumor Necrosis Factor-alpha Blockers for CRPS

Not Recommended.

TNF-alpha blockers are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: TNF-alpha blockers have not been evaluated in quality studies for CRPS.[223, 224] There is one low quality trial that was prematurely terminated [363]. These agents are minimally invasive, have significant adverse effects, are high cost, and in the absence of quality evidence of efficacy, they are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in

CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 low-quality RCT incorporated into this analysis (Appendix 4).

Intravenous immunoglobulin has been used for treatment of CRPS [364][365][366][367]. Retrospective studies of plasma exchange transfusion have been reported [368].

Intravenous Immunoglobulin (IVIG) for CRPS

Recommended.

Intravenous immunoglobulins are selectively recommended for treatment of CRPS.

Strength of Evidence **– Recommended, Evidence (C)**
Level of Confidence – Moderate

Indications:	Severe CRPS had pain intensity greater than 4 on an 11-point (0 to 10) numerical rating scale; having had CRPS for 6 to 30 months; refractory to treatment with all of: strengthening exercises, aerobic exercises, acetaminophen, NSAIDS, tricyclic antidepressants, and either gabapentin or pregabalin [366].
Benefits:	Pain reduction. Theoretical potential to increase exercise compliance and functional use.
Harms:	Headaches, pain increase, infusion site reaction, worsening eczema, chills, tiredness, dizziness, abdominal pain, depression, symptoms in opposite hand.
Frequency/Dose/Duration:	IVIG, 0.25 g/kg for one day and the same dose repeated on the following day [366]. Frequency of a second course is unclear, as the sole quality trial lasted one month and the data suggest at least some of the benefits were still present at 30 day
Indications for Discontinuation:	Completion of one course and assessment for objective benefits. Consideration of additional treatments based on progressive functional gains.
Rationale:	Intravenous Immunoglobulin (IVIG) has been evaluated in one high quality crossover RCT for CRPS which suggested significant pain reductions [366]. However, the trial has not been replicated, was small in size, and reported no intermediate or long-term follow-up. IV immunoglobulin is invasive, has adverse effects, is high cost, has limited evidence of efficacy and is thus highly selectively recommended pending further studies.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome,

reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 high-quality RCT incorporated into this analysis.

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Goebel, 2010 (score=8.0)	CRPS	Crossover RCT	Sponsored by University College London Hospitals/University College London. No mention of COI.	N = 13 patients with long-standing CRPS.	Mean age: 41 Sex (M:F) 3:10	Group 1 (N =7) received intravenous immunoglobulin (IVIG) for their first intervention. After a 28 day washout period, a second intervention of saline was administered. vs Group 2 received a saline intervention first. After a 28 day washout period, an IVIG intervention was administered. (N =)	8 weeks	An average decrease of 1.55 units in pain scores after IVIG compared with saline ($P < 0.001$).	"IVIG, 0.5 g/kg, can reduce pain in refractory CRPS. Studies are required to determine the best immunoglobulin dose, the duration of effect, and when repeated treatments are needed.."	Quite small sample size, highly selective exclusion. Data suggest immunoglobulin is superior to saline for pain.

Vitamin C for Prevention of CRPS in Patients with Wrist Fractures, Extreme Trauma, or High Risk for CRPS

No Recommendation.

There is no recommendation for or against vitamin C for preventing CRPS in patients with fractures and, by analogy, for other extremity trauma, or in patients at high risk for CRPS (i.e., from surgical release for Dupuytren's contracture).

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are 3 moderate- and high-quality trials with conflicting evidence. Two are by the same author suggesting vitamin C of at least 500mg/day is effective compared with placebo for prevention of CRPS in wrist facture patients [369] [292]. There was no incremental benefit of 1.5g over 500mg/day [292]). One trial suggested lack of efficacy among fracture patients (Ekrol 14). Vitamin C is not invasive, has low adverse effects, is low cost, but since it has conflicting quality evidence of efficacy for prevention of CRPS, there is no recommendation.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 3 high- and moderate-quality RCTs incorporated into this analysis.

Evidence for the Use of Vitamins

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Zollinger 2007 (score = 8.0)	Vitamins	RCT	Sponsored by Stichting Achmea Slachtoffer en Samenleving. No COI.	N = 416 mostly elderly females with 427 wrist fractures	75 males, 341 females; Mean age Vit C: 62.7±16.8, Placebo 61.4±18.	Placebo (n = 99) vs. vitamin C 200, 500, or 1,500mg a day (n = 317) for 50 days for prevention of CRPS.	Baseline, 1 wk, 4-5 wks, 6-7 wks, 12 wks, 26 wks.	Risk for developing CRPS 10.1%, 4.2%, 1.8%, 1.7%. In 500mg group, RR = 0.17.	"Vitamin C reduces the prevalence of complex regional pain syndrome after wrist fractures. A daily dose of 500mg for fifty days is recommended."	Nutritional status of population not apparent, but as it is the Netherlands, it is expected to be comparable to U.S. Data suggest efficacy.
Ekrol 2014 (score = 7.5)	Vitamins	RCT	Sponsored by the Chief Scientist's Office for Scotland and the Scottish Orthopaedic Research Trust into Trauma (SORT-IT).	N= 336 adults with displaced or non-displaced distal radial fractures.	90 males, 246 females; Mean ages Vitamin C displaced 58±20, placebo displaced 62±18, nondisplaced vitamin C 51±19, nondisplaced placebo 54±21.	Stratified by displaced and nondisplaced fracture. Placebo vs. vitamin C 50mg QD for 50 days.	Baseline, 6, 12, 26, 52 weeks.	(Scores displaced VC/placebo; nondisplaced VC/placebo) CRPS (1.3/1.4; 0.7/0.6). CRPS scores at 6 wks >3 (33/35; 27/13,p=0.022). No differences in other outcomes at 52 wks.	"This study demonstrated no significant difference at one year in the DASH score, other functional outcomes, the rate of CRPS, or osseous healing of nondisplaced or diplaced distal radial fractures treated with vitamin C compared with placebo."	Data suggest lack of efficacy for time to heal fracture. Data also suggest higher pain, complications, and no prevention of CRPS.
Zollinger 1999 (score = 7.5)	Vitamins	RCT	No mention of sponsorship or COI.	N = 123 adults with 127 wrist fractures	25 males, 98 females; Mean age Vit C: 57 (27-88) Placebo: 60 (24-85)	Placebo (n = 66) vs. 500mg vitamin C daily (n = 57) for 50 days for prevention of CRPS.	Patients were assessed after 1 week, 4–5 weeks (when the plaster cast was removed), 6–7 weeks, 12 weeks, and 26 weeks.	Risk for RSD in vitamin C group was RR = 0.17.	"[V]itamin C was associated with a lower risk for RSD after wrist fractures. Our hypothesis is that this beneficial effect of prophylaxis would be useful in other forms of trauma."	Co-interventions not well controlled such as type of exercise/therapy. Vitamin C in did not evaluated. Data suggest evidence of efficacy.

Mannitol for Treatment of CRPS

Not Recommended.

Mannitol is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – Low

Rationale:	Mannitol has been evaluated in one moderate quality trial and found to be ineffective [370]. Mannitol is invasive, has adverse effects, is moderate cost, but has been shown to be ineffective and is thus not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 moderate-quality RCT incorporated into this analysis.

Evidence for the Use of Mannitol

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Perez 2008 (5.0)	CRPS	RCT	No mention of COI. Supported by the Pain Knowledge Center Maastricht.	N = 41 with CRPS I in either 1 arm or 1 leg	33 female, 8 male. Mean age 45.3 years	10% mannitol IV in 1 L 0.9% NaCL for 4 hours for 5 consecutive days (N = 22) or placebo of 0.9% NaCL in equal volumes (N = 19)	2, 6, and 9 weeks	Visual analog scale (VAS) pain scores for T2, T6, and T9: Max – placebo 71.1, 63.3, 62.2, mannitol 68.5, 67.8, 63.3, Min – placebo 46.2, 45.1 45.1, mannitol 50.6, 47.3, 49.7. VAS diff for placebo and mannitol, respectively: T0 vs T2 - -1.1, 2.5, T0 vs T6 0.0, 5.8, T0 vs T9 -0.1, 3.4. No significant differences found (P > 0.05)	"In summary, we conclude that intravenous administration of 10% mannitol is not more effective than placebo in reducing complaints for CRPS I patients and provides no addition to already-established interventions for CRPS I."	No meaningful differences between groups. High co-intervention use, not well controlled.

Opioids

See Opioids guideline.

Allied Health Interventions

Hyperbaric Oxygen for CRPS

No Recommendation.

There is no recommendation for or against the use of hyperbaric oxygen for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There is one moderate-quality study of HBO published in 2004 of 45 days without followup that suggested potential efficacy for treatment of CRPS.[371] HBO is not invasive, has generally low adverse effects, is high cost and has one study that is somewhat suggestive. There is no recommendation for or against its use in CRPS patients until results of the single available study have been independently shown to be reliable and valid with sufficient follow-up. There are medications with proven efficacy that should be combined with a program of exercises that are recommended prior to consideration of this intervention.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 moderate-quality RCT incorporated into this analysis.

Evidence for the Use of Hyperbaric Oxygen

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Kiralp 2004 (score = 6.5)	Hyperbaric oxygen for CRPS	RCT	No mention of COI or sponsorship	N = 71 with post-traumatic CRPS Type I of upper extremity; disease duration 1.5 months	Mean age: 30.4 years. 49 males, 22 females	Hyperbaric oxygen (n = 37) vs. Room air (n = 34) in Turkey. Each group treated with 15 sessions for 90 minutes. PT not prescribed, rather paracetamol 500mg TID given for pain relief and to control for co-interventions.	Follow up period: not mentioned.	Significant reductions in VAS scores, increases in ROM, reductions in wrist circumference HBO vs. room air group. HBO had reductions in pain, edema, ROM, "significantly better results with the exception of wrist extension." Wrist extension (degrees): NS between groups all time periods.	"HBO is an effective and well-tolerated method for decreasing pain and edema and increasing the range of motion (ROM) in patients with CRPS."	No mention of co-intervention other than medication and PT. HBO decreased symptoms compared to sham.

Magnets and Magnetic Stimulation for CRPS

Not Recommended.

Magnets and magnetic stimulation are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There is no quality evidence suggesting efficacy of magnets to treat CRPS and thus they are not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 moderate-quality RCT incorporated into this analysis.

Evidence for the Use of Magnets and Magnetic Stimulation

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Durmus 2004 (score = 6.0)	Use of magnets or magnetic stimulation	RCT	No mention of COI or sponsorship	N = 40 with CRPS Type I subsequent to trauma (Colles fracture)	Mean age: 39.12 years, 20 males, 20 females	Compared electromagnetic field treatment administered with calcitonin and exercise. All patients pre-treated with calcitonin (100 units) and half (Group 1, n = 20) received electromagnetic field treatment 5 times a week for 6 weeks. vs. Other half (Group 2, n = 20) received placebo treatment by being placed in same device without it being switched on (60 minutes a session).	No mention of follow up	VAS-activity: EFT (4.25±2.10) vs. placebo (3.00±2.20), p= 0.033. NS between groups for all other outcomes.	"The absence of a significant difference between the two groups in the assessment parameters has been interpreted as evidence that electromagnetic field treatment does not provide additional benefit to calcitonin and exercise treatment."	Blinding measures not well described. Baseline differences in pain scales not significant, but treatment group has higher baseline pain values than controls, and post-treatment those differences disappeared, so suggestion that reduction in pain ratings is significant may be misleading.

Occlusal Splint for CRPS

Not Recommended.

Occlusal splints are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	One moderate quality trial reported a lack of efficacy for nocturnal occlusal splinting for treatment of CRPS who also had temporomandibular joint issues [372]. These interventions are not invasive, have minimal adverse effects, are moderately costly, but in the absence of evidence of efficacy are not indicated for the treatment of CRPS. Occlusal splints may have other uses for which they are indicated (temporomandibular joint problems).
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 moderate-quality RCTs incorporated into this analysis.

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Fischer 2008 (5.0)	CRPS	RCT	No mention of COI. Supported by grant from the German Society of Manual Medicine-Forschungsgemeinschaft für Arthrologie und Chirotherapie (FAC).	N = 20 with CRPS according to International Association for the Study of Pain	15 female, 5 male. Mean age 48 years	An occlusal splint (OS) was fitted for the intervention group (N = 10) and instructions given to wear this through the night and 3 hours a day for 7 weeks. Comparison group (N = 10) received no treatment. All patients received occupational (2 X week for 30 min) and physical therapy (2 X week for 30 min) to treat CRPS.	Follow-up consisted of self-report. Participants rated minimum, average, and maximum pain related to CRPS daily, with self-administration of the Short Form 36 Health Survey (SF-36) at baseline and 7 weeks post treatment.	NRS pain score mean values: Maximum pain intensity – OS 7.0±1.4 group, Control 7.0±2.1, Minimum pain intensity – OS 5.0±1.9, Control 4.1±2.0, Average pain intensity – OS 6.0±1.6, Control 5.7±1.7. No significant difference from baseline to end of treatment - maximum pain (P=0.708), minimum pain (P=0.100), and average pain (P=0.736)	"The present pilot study indicated that the use of OS for 7 weeks has no impact on CRPS-related pain but improved signs and symptoms of TMD pain. Future studies should include an active control group and evaluate if long-term changes in measures of oral health could have an impact on general health in CRPS-related pain."	Small sample size (n=20). Proof of concept study, not powered to detect differences. However, data suggest lack of efficacy for treatment of CRPS.

Taping and Kinesiotaping for CRPS

Not Recommended.

Taping and kinesiotaping are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality trials of taping and kinesiotaping for treatment of CRPS. Taping is not invasive, may have potential adverse effects among those who do not tolerate it or the adhesives, is moderate to high cost in aggregate, has no evidence of efficacy and thus is not recommended for treatment of CRPS.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating taping and kinesiotaping for the treatment of CRPS.

Acupuncture for CRPS

No Recommendation.

There is no recommendation for or against acupuncture for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality trials evaluating acupuncture for treatment of CRPS. (One small study found no differences between sham and classic Chinese acupuncture.[243]) The majority of quality trials on various chronic pain disorders have demonstrated that there is no benefit of traditional Chinese acupuncture over other types of acupuncture. (see other guidelines, e.g., Low Back, Cervical Spine)

Acupuncture when performed by experienced professionals is minimally invasive, has minimal adverse effects, is moderately costly but as it lacks evidence of efficacy for treatment of CRPS, there is no recommendation.

Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 18 high- or moderate-quality RCTs on low back pain incorporated into this analysis (see guideline on Low Back Disorders for these studies). There is one moderate-quality RCT incorporated into this analysis. There are 6 low-quality RCTs,[252, 373-377] in Appendix 4. Trials enrolling only elderly patients,[378-381] or patients with lower urinary tract symptoms[382] or chronic pancreatitis[383] patients were not included.

Evidence for the Use of Acupuncture

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Korpan 1999 (score = 5.0)	Acupuncture	RCT	No mention of COI or sponsorship	N = 14 with early RSD (1 to 6 months duration)	Mean age: 51.8 years, 10 females, 4 males	Double-blind design assessed classic Chinese acupuncture (5 times a week for 3 weeks) vs. sham acupuncture.	1, 3 and 6 months after completion of acupuncture treatment	No significant results between groups.	"No differences between sham and treatment group could be recognized."	Possibility results may have been positive for both if sham group was in fact an active control. Blinding not well described.

Cryotherapies for CRPS

Not Recommended.

Cryotherapies are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies of cryotherapies for treatment of CRPS. Cryotherapies are not invasive, have negligible adverse effects, are low cost when self-applied, but are generally not well tolerated by CRPS patients and thus are not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating cryotherapies for the treatment of CRPS.

Self-application of Heat Therapy for CRPS

Recommended.

Self-application of low-tech heat therapy is recommended for treatment of CRPS.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	CRPS sufficient to require treatments beyond exercises and potentially medication. Applications should be home-based as there is no evidence for efficacy of provider-based heat treatments. Primary emphasis should generally be on compliance with progressive strengthening and aerobic exercises as part of a functional restoration program elements, rather than on passive treatments in patients with chronic pain which could be detrimental.
Benefits:	Mild improvements in symptoms
Harms:	Misplaced focus on passive modalities instead of active exercises, which may hinder progress.

Frequency/Dose/Duration: Self-applications may be periodic, generally up to a few times a day. Education regarding home heat application should be part of the treatment plan if heat has been effective for reducing pain.

Indications for Discontinuation: Intolerance, increased pain, development of a burn, other adverse event.

Rationale: There are no quality studies of heat therapies for treatment of CRPS. Heat therapies are not invasive, have negligible adverse effects, are low cost when self-applied, seem to be helpful for some patients and thus are selectively recommended. The main hazard is misplaced focus on passive modalities instead of active, progressive exercises. Healthcare provider administered heat therapies are generally not indicated.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating heat therapies for the treatment of CRPS.

Diathermy for CRPS

Not Recommended.

Diathermy is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality studies of diathermy for treatment of CRPS. It has not been shown to be more effective than placebo diathermy in studies of the spine (see Low Back Disorders). Diathermy is not invasive, has negligible adverse effects, is moderately costly, has no quality evidence of efficacy for CRPS and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies.

We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 2 moderate-quality RCTs (one with two reports) incorporated into this analysis which were primarily designed to evaluate the efficacy of manipulative therapies and utilized diathermy as a control.[225-229] There are no quality studies evaluating diathermy for the treatment of CRPS.

External Radiation for Sympathetic Blockade for CRPS

Not Recommended.

External radiation for sympathetic blockade is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – Low

Rationale: While external radiation has been used to treat CRPS, available quality studies suggest it is not effective.[230] External radiation is not invasive, has adverse effects, is moderate to high cost, but has no evidence of efficacy for CRPS and is thus not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 moderate-quality RCT/crossover trial incorporated into this analysis.

Evidence for the Use of External Irradiation for Sympathectomy

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Basford 2003 (score = 6.5)	Use of external irradiation for Sympathectomy	RCT/Crossover Trial	No mention of COI or sponsorship	N = 6 with unilateral upper extremity CRPS I	Mean age: 40 years, 1 males, 5 females.	Transcutaneous irradiation of right stellate ganglion with linearly polarized 0.6-1.6μm light vs. no medication or other exposures (Phase I, n = 6 with normal neurological exams). Phase II: double-blinded evaluation of active and placebo radiation in 12 subjects (6 upper extremity CRPS I/6 "normal" controls). Skin temperature, heart rate, sudomotor function, vasomotor tone monitored before, during, 30 minutes following irradiation. Analgesic and sensory effects assessed over same period and 1 and 2 weeks later.	Follow up: not mentioned	Pain not statistically significantly reduced. Authors noted that 3 of 6 CRPS I subjects, but no control subjects, experienced sensation of warmth following active irradiation, and 2 CRPS I subjects reported more than 50% pain reduction.	"However, four noted minimal or no change and improvement did not reach statistical significance for the group as a whole. No statistically significant changes in autonomic function were noted."	Tiny sample size. No adverse consequences observed. Study found preliminary evidence that external radiation for purposes of producing a permanent sympathetic block is technically possible. Likely underpowered to detect pain reduction. Study does not show evidence of efficacy of intervention, especially long-term improvements.

Infrared Therapy for CRPS

Not Recommended.

Infrared therapy is not recommended for treatment of CRPS

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies of infrared therapy for treatment of CRPS. It has not been shown to be more effective than placebo in studies of other disorders. Infrared therapy is not invasive, has negligible adverse effects, is moderately costly, has no quality evidence of efficacy for CRPS and thus is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating infrared therapy for the treatment of CRPS.

Low-level Laser Therapy for CRPS

No Recommendation.

There is no recommendation for or against low-level laser therapy for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	Studies conflict on the efficacy of low-level laser treatment (LLLT) for various disorders (see Low Back Disorders and Shoulder Disorders Guidelines). There are no quality studies of LLLT for treatment of CRPS. It has not been shown to be consistently more effective than placebo in studies of other disorders. LLLT is not invasive, has negligible adverse effects, is moderately costly, has no quality evidence of efficacy for CRPS and thus there is no recommendation.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly;

systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 4 high-and moderate-quality[233-236] RCTs incorporated into this analysis (see Low Back Disorders guideline for studies). There is also 1 moderate-quality RCT for myofascial pain incorporated into this analysis.[237] There are no quality studies evaluating LLT for the treatment of CRPS.

Manipulation for CRPS

No Recommendation.

There is no recommendation for or against manipulation for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality studies of manipulation or mobilization for treatment of CRPS. Manipulation is not invasive, has low adverse effects in experienced hands, is moderate to high cost in aggregate, but with the lack of quality evidence of efficacy for treatment of CRPS, there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are moderate-quality RCTs incorporated into this analysis. There are 23 moderate-quality studies (5 with multiple reports) in the Low Back Disorders guideline. There also are 11 systematic reviews, 1 guideline, and 12 low-quality RCTs included in the Appendix of the guideline on Low Back Disorders. . There are no quality studies evaluating manipulation or mobilization for the treatment of CRPS.

Massage for CRPS

No Recommendation.

There is no recommendation for or against the use of massage for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies of massage for treatment of CRPS. Massage is not invasive, has low adverse effects, is moderate to high cost in aggregate, but with the lack of quality evidence of efficacy for treatment of CRPS, there is no recommendation. There also is no recommendation for use of mechanical massage devices for massage.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating massage for the treatment of CRPS.

Myofascial Release for CRPS

Not Recommended.

Myofascial release is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies of myofascial release for treatment of CRPS. Myofascial release is not invasive, has low adverse effects, is moderate to high cost in aggregate and in the absence of quality evidence of efficacy it is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in

CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating myofascial release for treatment of CRPS.

Reflexology for CRPS

Not Recommended.

Reflexology is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality studies of reflexology for treatment of CRPS. Reflexology is not invasive, has negligible adverse effects, is moderate cost in aggregate, has no quality evidence of efficacy for CRPS and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 moderate-quality RCT incorporated into this analysis. There are no quality studies evaluating reflexology for the treatment of CRPS.

Electrical Therapies

High-voltage Galvanic Therapy for CRPS

Not Recommended.

High-voltage galvanic therapy is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality studies of high-voltage galvanic for treatment of CRPS. High-voltage galvanic is not invasive, has low adverse effects, is

moderately costly, but in the absence of evidence of efficacy it is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 moderate-quality RCT evaluating high-voltage galvanic stimulation for chronic neck pain, but no quality studies evaluating high-voltage galvanic for treatment of LBP, neuropathic pain, CRPS, trigger points/myofascial pain or other chronic persistent pain.

H-Wave® Device Stimulation for CRPS

No Recommendation.

There is no recommendation for or against H-Wave® Device Stimulation for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – Low

Rationale: There are no quality studies of H-Wave® Device Stimulation for treatment of CRPS. H-Wave® Device Stimulation is not invasive, has low adverse effects, is high cost, does actively contract muscles which is a major problem with CRPS patients, but in the absence of evidence of efficacy there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating H-Wave® Device Stimulation for treatment of chronic LBP, neuropathic pain, CRPS, trigger points/myofascial pain, or other chronic pain conditions.

Interferential Therapy for CRPS

Not Recommended.

Interferential therapy is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies of interferential therapy for treatment of CRPS. Interferential therapy is not invasive, has low adverse effects, is moderately costly, but in the absence of evidence of efficacy it is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating infrared therapy for the treatment of CRPS.

Iontophoresis for CRPS

Not Recommended.

Iontophoresis is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies of iontophoresis for treatment of CRPS. Iontophoresis is not invasive, has low adverse effects, is moderately costly, but in the absence of evidence of efficacy it is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from

other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating iontophoresis for treatment of chronic LBP, neuropathic pain, CRPS, trigger points/myofascial pain or other chronic persistent pain (see Elbow Disorders guideline for studies on iontophoresis for lateral epicondylalgia).

Microcurrent Electrical Stimulation for CRPS

Not Recommended.

Microcurrent electrical simulation is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality studies of microcurrent electrical stimulation for treatment of CRPS. Microcurrent electrical stimulation is not invasive, has low adverse effects, is moderately costly, but in the absence of evidence of efficacy it is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating microcurrent electrical stimulation for treatment of chronic LBP, CRPS, trigger points/myofascial pain, or other chronic pain conditions.

PENS for CRPS

Not Recommended.

PENS is not recommended outside of research settings for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: PENS has been evaluated in small scale, short-term studies of chronic pain patient, but no quality studies are available for CRPS. PENS is

minimally invasive, has low adverse effects, is moderately costly, but in the absence of evidence of efficacy it is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 6 moderate-quality RCTs incorporated into this analysis (see Low Back Disorders guideline for these studies). There is also 1 guideline and 2 low-quality RCTs in the Appendix of the guideline on Low Back Disorders. There are no quality studies evaluating PENS for treatment of CRPS or trigger points/myofascial pain.

Sympathetic Electrotherapy for CRPS

Not Recommended.

Sympathetic electrotherapy is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There are no quality studies identified and there is no quality evidence of efficacy. Other modalities have been shown to be effective in the treatment of CRPS and other patients with chronic pain. Sympathetic electrotherapy is not invasive, likely has relatively minor adverse effects, is costly, but in the absence of quality evidence of efficacy is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating sympathetic electrotherapy for treatment of patients with chronic pain, including CRPS and other chronic pain conditions.

TENS for CRPS

Not Recommended.

TENS is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality studies of TENS for treatment of CRPS. TENS is not invasive, has low adverse effects, is moderately costly, but in the absence of evidence of efficacy it is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 5 high- or moderate-quality RCTs or crossover trials incorporated into this analysis. There are 2 low-quality RCTs[271, 272] in Appendix 4. See Low Back Disorders guideline for additional studies.There are no quality studies evaluating TENS for the treatment of CRPS.

Injection Therapies

Botulinum Injections for CRPS

No Recommendation.

There is no recommendation for or against the use of botulinum injections for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There is no quality evidence for the use of botulinum injections to treat CRPS. These injections are invasive, have adverse effects including reported deaths, and are costly; thus, there is no recommendation for or against their use.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies.

We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is one low-quality RTC (Safapour 2011) in Appendix 4.

Intrathecal Baclofen for CRPS

Recommended.

Intrathecal baclofen is selectively recommended for treatment of dystonia associated with CRPS.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Indications:	Highly limited indication of severe dystonia accompanying severe CRPS.
Benefits:	Reduction in dystonia
Harms:	Dizziness, drowsiness, sedation, confusion, nausea, vomiting, headache, seizures. Also has adverse effects related to intrathecal administrations of medications.
Frequency/Dose/Duration:	Various regimens have been used including daily boluses of 25, 50, or 75µg of baclofen [384].
Indications for Discontinuation:	Intolerance, adverse effects, resolution of dystonia.
Rationale:	Intrathecal baclofen has been studied for purposes of treating severe dystonia in one very small high-quality study [384]; [385]. Dystonia is not part of the typical case criteria for CRPS, raising questions about the patient population studied and generalizability to other CRPS patients. Nevertheless, the results were dramatic. Intrathecal baclofen is invasive, has significant complications, and is high cost. However, it may be indicated for a very narrow therapeutic indication of severe dystonia following a diagnosis of CRPS.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is one high- and one moderate-quality RCT incorporated into this analysis.

Evidence for the Use of Intrathecal Baclofen

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
van Hilten 2000 (score = 8.0)	Intrathecal baclofen	RCT	No mention of COI or sponsorship	N = 7 females previously diagnosed with CRPS with multifocal or generalized tonic dystonia (symptoms for a mean of 13 years)	Mean age: 45 years; 7 females	Compared daily boluses of 25, 50, or 75µg of baclofen vs. placebo. Patients followed from 0.5 to 3 years (average 1.7 years).	Patients were followed for 0.5 to 3 years.	Per patient assessments, injections of 50 and 75 micrograms baclofen resulted in significant decreases in severity of dystonia vs. placebo and to 25 micrograms. Treatment highly effective for dystonia in hands, but not lower extremities. Pump implanted in those experiencing at least 50% improvement above placebo response. During continuous therapy, 3 regained normal hand function, and 2 of 3 regained ability to walk (1 only indoors). In 1 who received continuous therapy, pain and violent jerks disappeared and dystonic posturing of arm decreased. In 2, spasms or restlessness of legs decreased without any change in dystonia.	"In some patients, the dystonia associated with reflex sympathetic dystrophy responds markedly to intrathecal baclofen."	Data suggest intrathecal baclofen reduces dystonia in CRPS over short term. Pumps then used. Not randomized.
Van der Plas 2011 (6.0)	Intrathecal baclofen	Crossover RCT	Sponsorsed by Medtronic sàrl, Tolochenaz Switzerland. No COI.	N = 14 patients with CRPS-related dystonia	Mean age 45.5. 1 males, 13 females.	Slower infusion rate delivery (SIRD) system of intrathecal baclofen (ITB) (N = 7), vs four-times faster infusion rate delivery (FIRD) of ITB (N = 7).	Follow-up at week 2, 3 and 5.	Following 2 weeks of 3 mg/mL daily of baclofen in the SIRD group, and .75 mg/mL of baclofen daily in the FIRD group, there was a week wash-out period before groups switched procedures. After group cross-over, the same procedures continued for another 2 weeks. No statistically significant results were seen comparing FIRD and SIRD in dystonia, pain, or secondary outcomes. One exception of secondary outcomes came from significantly higher adverse events (P = 0.01) during FIRD.	**"Increasing the IR at a fixed daily dose is not associated with improvement of dystonia or pain but warrants further investigation in patients in whom side effects prevent further dose escalation. "**	Small sample size crossover study demonstrated significant differences in favor of intrathecal baclofen infused at a high rate.

Intrapleural Bupivacaine Infusions for CRPS

Not Recommended.

Intrapleural bupivacaine infusions are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	Intrapleural bupivacaine infusions have not been evaluated in sizable quality studies for diagnostic, prognostic, or treatment purposes for CRPS patients. These infusions are invasive, have potential adverse effects, are costly, and in the absence of quality evidence of efficacy, there is no recommendation.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating intrapleural bupivacaine for treatment of patients with CRPS.

Lidocaine Infusion for CRPS

No Recommendation.

There is no recommendation for or against the use of lidocaine infusions for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	One low quality study suggests short term improvements in some measures. However, there is no quality evidence of efficacy for treatment of CRPS patients. There is no evidence that these infusions result in a sustained decrease in pain medication requirements, reported pain, or an increase in overall function. Lidocaine infusions may be reasonable for select patients (e.g., CRPS) for diagnostic purposes. Repeated infusions without objective evidence of prolonged efficacy and functional improvement are not recommended. Some centers reportedly are using multi-day inpatient infusions of lidocaine for patients with CRPS. There are no large, quality studies evaluating the safety and effectiveness of this treatment. Lidocaine infusions have not been evaluated in sizable, quality studies for diagnostic, prognostic, or treatment purposes. Lidocaine infusions are invasive,

have adverse effects [276, 277, 279], are moderate to high cost and in the absence of quality evidence of efficacy there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 3 low-quality RCTs in Appendix 4.

Stellate and Other Ganglion Blocks for CRPS

Recommended.

Stellate ganglion blocks and other ganglion blocks corresponding to the body region afflicted by CRPS are recommended for treatment of acute or an acute flare-up of CRPS as an adjunct to a functional restoration approach.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications: Acute CRPS or an acute flare up of CRPS that has not responded or is inadequately controlled with progressive strengthening, graded exercise, physical therapy/occupational therapy and medications. Should be performed when it is integrated into a comprehensive treatment program emphasizing functional restoration.

Benefits: Potential improved ability to tolerate and accomplish progressive exercise

Harms: Complications of the procedure, medicalization, externalization away from a focus on active exercise.

Frequency/Dose/Duration: Additional blocks if clear objective evidence of functional improvement.

Indications for Discontinuation: Resolution, adverse effects, intolerance, failure to improve or non-compliance with treatment recommendations.

Rationale: There are small studies that have evaluated the efficacy of this treatment strategy[386].There is no sizeable study of high-grade evidence. The available evidence suggests that at best, there is a modest degree of improvement assuming larger studies are able to detect any improvement at all. These injections also are unlikely to

	provide long-term benefits unless promptly coupled with graded exercises. Sympathetic blocks are invasive and have some complications. One block is moderately costly, but repeated blocks are high cost. A sympathetic block is recommended for highly select patients who may benefit from blockade to facilitate involvement and advancement in a functional restoration approach.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is 1 high-quality crossover trial incorporated into this analysis. There are 2 low-quality RCTs in Appendix 4.

Evidence for the Use of Regional Sympathetic Blocks

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Price 1998 (score = 8.5)	Stellate Ganglion Blocks for CRPS	Crossover Trial		N = 7 with CRPS Type I or II (IASP criteria); duration 18 months to 7 years (median 21 months)		Compared 15mL 1% lidocaine followed by 10mL 0.25% bupivacaine with saline stellate ganglion (n = 4) vs. lumbar sympathetic blocks (n = 3). Follow-ups at 15, 30, 45, 60, 75, 90 minutes; journal kept for 7 days.		No significant differences found.	"[D]uration of pain relief is affected by injection of local anesthetics into sympathetic ganglia. These results indicate that both magnitude and duration of pain reduction should be closely monitored to provide optimal efficacy in procedures that use local anesthetics to treat CRPS."	Retrospective analysis found mean duration of relief for those who achieved Horner's syndrome finding was 52.3±103.9 vs. 1.1±1.7 hours for those who did not. Skin surface temperature change findings similar; 7 day follow-up. Very small sample size. Data suggest lidocaine/bupivacaine sympathetic ganglia blocks superior to placebo for very short term.

Guanethidine Bier Blocks for CRPS

Strongly Not Recommended.

Bier blocks using guanethidine are strongly not recommended for treatment of CRPS.

Strength of Evidence – **Strongly Not Recommended, Evidence (A)**
Level of Confidence – High

Rationale:	All of the highest quality trials suggest lack of efficacy of guanethidine bier blocks for CRPS [388][389][390][391]. The lowest quality study reported no differences between guanethidine and reserpine [392]. Guanethidine blocks are invasive, have adverse effects, are at least moderate cost and have strong evidence of lacking efficacy, thus they are not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are high and moderate-quality RCTs or crossover trials incorporated into this analysis.

Phentolamine Bier Blocks for CRPS

No Recommendation.

There is no recommendation for or against the use of bier blocks using phentolamine for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale:	There are no quality trials of phentolamine bier blocks for CRPS. Phentolamine blocks are invasive, have adverse effects, are at least moderate cost and have no evidence of efficacy, and thus there is no recommendation.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from

other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating phentolamine bier blocks for the treatment of CRPS.

Bretylium Bier Blocks for CRPS

Recommended.

Bier blocks using bretylium are recommended for treatment of severe cases of CRPS.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications:	Severe CRPS that has not responded or is inadequately controlled with progressive exercise, bisphosphonates, glucocorticosteroids, NSAIDs, active exercise, physical therapy/occupational therapy, and potentially mirror therapy. It may be reasonable to attempt control with clonidine, anti-convulsants, tricyclic anti-depressants, or hyperbaric oxygen prior to consideration of bretylium. Should be performed as an adjunct to improve physical capabilities through a functional restoration program.
Benefits:	Theoretical potential to tolerate and advance progressive exercise program.
Harms:	Elevated blood pressure, hypotension, dizziness, nausea, vomiting, dysrhythmia, rare risk of fatality
Frequency/Dose/Duration:	Lidocaine 40ml with bretylium 1.5mg/kg. [393]. Additional blockades should be based on objective evidence of progressive improvement.
Indications for Discontinuation:	Resolution, adverse effects, intolerance, failure to improve, non-compliance.
Rationale:	There is one moderate quality trial of bretylium bier blocks suggesting efficacy for CRPS [393]. Bretylium blocks are invasive, have adverse effects, are at least moderate cost and have some evidence of efficacy, and thus they are selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is one moderate-quality RCT incorporated.

Methylprednisolone Bier Blocks for CRPS

Not Recommended.

Bier blocks using glucocorticosteroids are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Evidence (C)**
Level of Confidence – Low

Rationale: There is one moderate quality trial of methylprednisolone bier blocks suggesting lack of efficacy for CRPS [394]. Glucocorticoid blocks are invasive, have adverse effects, are at least moderate cost, have evidence of lacking efficacy, and thus they are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There is one moderate-quality RCT incorporated into this analysis.

Reserpine Bier Blocks for CRPS

Not Recommended.

Bier blocks using reserpine are not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There is one comparative trial suggesting comparable results between guanethidine and resperpine [392]. As there is evidence guanethidine is not superior to placebo, there is thus evidence suggesting reserpine is not likely effective. Reserpine blocks are invasive, have adverse effects, are at least moderate cost, have indirect evidence suggesting lack of efficacy, and thus they are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in

CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 4 high- or moderate-quality RCTs/crossover trials incorporated into this analysis on guanethidineThere is also 1 moderate-quality RCT/crossover trial on bretylium and 1 moderate-quality RCT on methylprednisolone incorporated into this analysis. There are no quality studies evaluating the use of phentolamine or reserpine for treatment of CRPS.

Brachial Plexus Blocks and Infusions for CRPS

No Recommendation.

There is no recommendation for or against the use of brachial plexus blocks and infusions for treatment of CRPS.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – Low

Rationale: There is one pilot RCT of brachial plexus blocks compared with stellate ganglion blocks [395], but there is no placebo control. The study suggests a need for a larger trial. Thus, there is no quality evidence that brachial plexus/neuraxial blocks and infusions alter the course of CRPS. Brachial plexus/neuraxial blocks have been reported in conjunction with active rehabilitation services in recalcitrant cases of CRPS. Brachial plexus/neuraxial blocks are invasive, require inpatient hospitalization, have significant adverse effects, and are costly. However, they are sometimes utilized in more severe cases where treatment options may be difficult and limited. Thus, there is no recommendation either for or against the use of these blocks and infusions.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating brachial plexus/neuraxial blocks and infusions for treatment of CRPS.

Evidence for the Use of Guanethidine, Bretylium, Methylprednisolone, Phentolamine, or Reserpine Bier Blocks

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Livingstone 2002 (score = 8.5)	Bier Blocks – Guanethidine	RCT	Funding by grants from Arthritis Research council.	N = 57 with CRPS Type 1, 9 weeks after an isolated closed Colles' fracture	Mean age 61.3 males 54 females	Serial intravenous regional blockade (IVRB) with 15mg of guanethidine in 30ml of 0.5% prilocaine (n = 27) vs. serial IVRB 30ml normal saline (n = 30) at weekly intervals; duration 6 months.	6 months.	Pain on exercise, at 1 week, favored placebo group (p = 0.035). Guanethidine group experienced greater amount of color change in hands (p = 0.015).	"[T]here is no benefit in using such blocks in early CRPS type 1 of the hand and also suggests that its use may delay the resolution of some features of the condition."	Data suggest lack of efficacy.
Jadad 1995 (score = 8.0)	Bier Blocks – Guanethidine	RCT/Crossover Trial	No mention of sponsorship or COI	N = 10 with RSD and at least 4 of following: persistent pain, hyperesthesia, edema, hyperhidrosis, color changes, radiographic evidence of Sudeck's atrophy, or history of injury	Mean age 58.25.4 males 12 females.	Saline vs. guanethidine low dose 10mg vs. guanethidine high dose 30mg for 3 sessions at weekly intervals. Study duration 4 weeks.	1 week.	No significant differences between groups.	"Patients in all groups reported less than 30% of the maximum possible relief during the first week after the injections, and on only two occasions (one saline and one guanethidine low dose) was relief reported for longer than a week. There was no evidence of a dose response for	Data suggest lack of efficacy.

									guanethidine. The use of guanethidine in IRSBs [intravenous regional sympathetic blockades] for patients with RSD was not supported by the systematic review or by the double-blind study."	
Ramamurthy 1995 (score = 6.5)	Bier Blocks – Guanethidine	RCT	Sponsorship by a grant from Ciba-Geigy corporation. No mention of COI	N = 57 with severe RSD/causalgia for upper extremity <3 months duration	Mean age 39.5. 24 males 33 females.	1 block (active drug for 2nd IVRB) (n = 20) vs. 2 Block (active drug on 2nd and 3rd IVRBs) (n = 19) vs. 4 block (active drug all IVRBs) (n = 18). At 4-day intervals, series of 4 IVRBs with either guanethidine or placebo in 0.5% lidocaine. Study duration 6 months.	6 months	Guanethidine group favored for PRI over placebo (p = 0.031).	"[T]herapeutic benefits provided by IVRB guanethidine were not different from those provided by the IVRB placebo. While pain and other symptoms tended to decrease over time, there was no relationship between the number of IVRB guanethidine blocks and relief of symptoms."	Blinding procedures not well described. Data suggest lack of efficacy.
Blanchard 1990 (score = 5.5)	Bier Blocks – Guanethidine	RCT	No mention of sponsorship or COI.	N = 21 with reflex sympathetic dystrophy of an upper or	Mean age 66.6. 12males 9	Saline 30-50ml (n = 12) vs. guanethidine 20mg UE and 30mg LE (n =	12 weeks.	No significant differences.	"There was significant pain relief in all three groups at 30 minutes.	Saline group's high rate of pain relief could be

				lower extremity	female s.	14) intravenous regional blocks with follow-ups for greater than 12 weeks.			There were no significant differences among the three groups in the degree of pain relief, the number of patients obtaining pain relief in the 30 minutes after the block, or the number of patients reporting more than 50% pain relief for more than 24 hour."	partially due to a mechanism of tourniquet-induced analgesia.
Hord 1992 (score = 5.5)	Bier Blocks – Bretylium	RCT/Crossover Trial	Sponsorship a grant from Journal of Bone and Joint Surgery of the Orthopedic Research and Education Foundation. No mention of COI.	N = 12 with history of RSD and Type II or III response on isolated cold stress testing	No mention of age or gender.	Each patient received 2 control treatments (local anesthetic only) and two treatments with Lidocaine 40ml with and without bretylium 1.5mg/kg for CRPS in random order.	40 days	Bretylium plus lidocaine produced more days with >30% pain relief than lidocaine alone. Temperature increase after IVR bretylium statistically significant.	"[I]ntravenous regional bretylium in combination with lidocaine blockade provides significant short-term pain relief when compared with IVR lidocaine for treatment of RSD."	Dropout rate high. Data suggest bretylium plus lidocaine may be superior to lidocaine IV block alone for RSD.
Taskaynatan 2004 (score = 6.0)	Bier Blocks – Methylprednisolone	RCT	No mention of sponsorship or COI.	N = 22 with CRPS in upper limbs in Turkey	Mean age 22.3. 22 men.	Intravenous regional anesthesia (bier block) methylprednisolone 40mg and lidocaine 10ml	follow-up for up to 1.5 months.	No significant differences between groups.	"Bier block with methylprednisolone and lidocaine in CRPS type 1 does not provide long-	Data suggest lack of efficacy.

						of 2% (n = 12) vs. placebo (n = 10) for 3 sessions. Treatment once a week			term benefit in CRPS, and its short-term benefit is not superior to placebo."	
Rocco 1989 (4.0)	Resperine vs guanethidine	RCT	No mention of sponsorship or COI.	N=12 patients who were diagnosed with reflex sympathetic dystrophy (RSD), or Causalgia, and experienced temporary pain relief by stellate or lumbar sympathetic block.	6 males, 6 females; Casaulgia mean age 29.8, RSD mean age 34.3.	Group 1 received 20 mg guanethidine in 50 ml or 0.5% lidocaine vs Group 2 received 1.25 mg reserpine in 50 ml 0.5% lidocaine vs Group 3 received 50 ml 0.5% lidocaine.	Each patient received each medication in one week intervals. Total of 6 weeks.	No difference in pain relief 90 min post tourniquet release between all groups. Reserpine average pain scores were higher, but not significant towards the end of the week. Side effects: 2 occurrences of depression, diarrhea, and nausea in reserpine. One occurrence of depression with guanethidine and control.	"[N]o difference was found in the therapeutic efficacy between reserpine and guanethidine. Regional intravenous reserpine or guanethidine is a reasonable alternative to stellate or lumbar sympathetic block."	Small sample size (n=12). No meaningful differences between groups.

Toshniwal, G 2007 (Score=4.5)	Brachial plexus blocks Vs Stellate ganglion blocks	RCT		N = 30 with CRPS type 1 of upper extremity.	17 females, 13 males; mean age 43.2	Continuous stellate ganglion (CSG) block a bolus of 10ml (5 + 5 mL) 0.25% bupivacaine was injected after negative aspiration. An elastomeric pump containing a solution of 0.125% bupivacaine 280 mL delivering a 2 mL/h was attached to the cannula. The bump was changed on day 5 and continuous infusion of 0.125% bupivacaine was maintained for 7 days. Vs Continuous Infraclavicular brachial plexus (CIBP) block. A bolus of 30 mL 0.25% Bupivacaine was injected through the catheter after negative aspiration.	4 weeks	Intensity of pain, unpleasantness were lower ($p < 0.05$) in the CIBP group at 30 min, 2/h, and 12/h vs the CSG. CIBP patients had reduction in deep pain scores at 30 minutes, 2 hours, 12 hours, and 24 hours. Dull pain score was lower in CIBP group at 2, 12, and 24 hours compared with CSG. No significant difference for all other components in NPSS. Improvement in quality of pain in both group. 100% of patients in CSG group and 91.7% of the patients in the CIBP group had	"This preliminary study suggests that both CSG and CIBP blocks may be feasible and effective interventional techniques in management of upper limb CRPS type I. Even though the overall satisfaction of the patients with either of the blocks was not significantly different, CIBP block is much easier to perform and manage. Hence, contrary to the present practice of limiting the use of somatic nerve blocks in those patients who have failed sympathetic block, we suggest that CIBP block can be used as a first line interventional technique for management of CRPS type I of	SmalSS (N = 30) Unequal randomization, possible randomization failure. Data suggest differences between treatment arms within 24 hours but no difference between 1 & 4 weeks.

						Catheter was connected to an elastomeric pump containing 0.125% bupivacaine 400mL delivering at 5mL/h. the pump was changed on day 3 and 6 continuous infusion of 0.125% bupivacaine was maintained for 7 days.		background pain with intermittent flare-ups. At week 4 four of 18 (22.2%) in CSG had back group pain with flare-ups vs 1 out of 12 (8.3%) in CIBP group. Constant back group pain was persisten in 11.1% (2/18) in CSG vs 8.3% (1/120 of CIBP. Occasional intermittent pain was 66/7% (12/18) in CSG vs 83.4% (10/12) in CIBP at 4 weeks. Overall patient satisfaction was 7.78 ± 1.309 in CSG vs 7.92 ± 0.996 in CIBP.	upper extremities."	

Surgical Considerations

Spinal Cord Stimulators for Short- to Intermediate-term Relief of CRPS

Recommended.

SCS implantation is recommended as an option for highly select CRPS patients who understand that this intervention has no quality evidence of greater than 3 year benefit during which time there is unequivocal patient commitment.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Low

Indications:	See Table 9.
Benefits:	Potential to engage and advance a progressive exercise program during the shorter term interval after implantation when there is some evidence of efficacy.
Harms:	Medicalization, paralysis, fatality. One-third of patients reportedly have adverse effects [396].
Frequency/Dose/Duration:	N/A
Indications for Discontinuation:	Resolution of pain, complications necessitating discontinuation of therapy or device removal, or loss of therapeutic effect.
Rationale:	There is evidence from one moderate-quality RCT that SCSs result in reduced pain for CRPS that is sustained over periods up to 3 years.[397-399] However, from Years 3 to 5, there was no statistically significant benefit from SCS compared to physical therapy[400]. Another trial suggested modest benefits at up to 3 months compared with sham/placebo (Kriek 16). Other case series report similar reductions in efficacy over time.[401] Importantly, there is no quality study that appears to compare SCSs with a multidisciplinary treatment program that emphasizes functional restoration. Indications for SCSs for CRPS have been published (see Table 9). A case series suggests social and psychological factors should be considered.[402] The literature also suggests that physical therapy alone has benefits, and also is of benefit when combined with use of SCSs. SCSs are invasive, have potential for adverse effects, and are high cost. SCSs are recommended for select patients (see Table 9).
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for

inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are 4 moderate-quality RCTs (one with 6 reports) incorporated into this analysis.[397-400, 403-405] There are 3 low-quality RCTs in Appendix 4.

Table 9. Selection Criteria for Implantable Spinal Cord Stimulator in a CRPS Patient*

1. Clear diagnosis of CRPS based on criteria that include objective measures, such as the Consensus Criteria.
2. Poor response to conservative treatment generally for at least 6 months,** including treatment in an experienced interdisciplinary clinic with proven good outcomes that included elements of a functional restorative program and for which the patient demonstrated good motivation.
3. Remedial surgery inadvisable or not feasible.
4. Major psychiatric disorders have been treated with expected responses. Somatization disorder not amenable to treatment will disqualify the patient for use of invasive procedures, as the risk of the procedure is higher than the expected success rate. The candidate should have a successful independent, psychological evaluation and a structured interview performed by a psychologist specialized in chronic pain management including appropriate psychometric testing (see Appendix 1). (The psychological evaluation should be performed by a practitioner who is not employed by the requesting or treating physicians).***
5. Willingness to stop inappropriate drug use before implantation.
6. No indication that secondary gain is directly influencing pain or disability complaints.
7. Ability to give informed consent for the procedure.
8. Successful results of at least 50% pain reduction from a trial of a temporary external stimulator of approximately 2-3 days and reduction of use of opioid medication or other medication with significant adverse effects or functional improvement such as return to work that may be evaluated by an occupational or physical therapist prior to and before discontinuation of the trial.

*Adapted from Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery*. 2006;58(3):481-96(; Lee AW, Pilitsis JG. Spinal cord stimulation: indications and outcomes. *Neurosurg Focus*. 2006;21(6):E3[38]; Segal R, Stacey BR, Rudy TE, et al. Spinal cord stimulation revisited. *Neurol Res*. 1998;20(5):391-6.(873)

**Some authors advocate earlier intervention,(37, 859); however, quality evidence is lacking.

***Presence of depression is common in patients with chronic pain, requires evaluation and may require treatment. Depression that is particularly severe may require treatment prior to assessing appropriateness of SCS, however, the presence of depression does not preclude SCS.

Evidence for the Use of Spinal Cord Stimulators

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Kelmer 2000, 2001, 2002, 2004, 2006, 2008 (score = 7.0)	Use of Spinal Cord Stimulators	RCT		N = 54 with CRPS diagnosed with IASP criteria;18 not working due to CRPS required to have at least a 50% pain reduction to be eligible for SCS implantation		Spinal cord stimulation (SCS) with physical therapy (graded exercises designed to improve strength, mobility, and function of affected hand or foot for 30 minutes twice a week with a minimum of 2 days in between sessions for 6 months duration) (n = 36) vs. PT alone (n = 18).		SCS had lower pain score at 6 months vs. PT group. Of 36 assigned to SCS and PT, 39% scored 6 for global perceived effort vs. 6% for PT-alone; 50% had at least 50% reduction in baseline pain score. Six of 24 SCS patients had 11 infection-related complications. Follow-up evaluation of same patient set described above noted no changes in detection and pain thresholds for pressure, warmth, or cold. (Kelmer 2001) The 2-year follow-up found health-related quality of life improved in group receiving spinal cord stimulation. (2002) Based on VAS scores, results for 2 years not appreciably different than at 6 months. Complications in 38%, mostly 1st year; 3 of 24 SCSs (12.5%) removed first 2 years. After apparent initial significant benefit 1st year, those with SCS gradually had increasing pain scores. By Year 3, while modest reductions in PT group, SCS of no statistically significant benefit. (2006)	"In carefully selected patients with chronic reflex sympathetic dystrophy, electrical stimulation of the spinal cord can reduce pain and improve health-related quality of life."	Content of PT not well described, nor if it differed among groups. Data suggest short- to intermediate-term improvements, but no long-term benefits.

North 2005 (score = 5.5)	Use of Spinal Cord Stimulators	RCT	No mention of sponsorship or COI.	N = 50 with surgical remediable nerve root compression and concordant complaints of persistent or recurrent radicular pain, with or without LBP after 1 or more lumbosacral spine surgeries	Mean age 57. 16 females 8 males.	Spinal cord stimulation (SCS) (n = 24) vs. repeated lumbosacral spine surgery (n = 26) for 3 years of follow-up.	2.9 years	Surgical treatment individualized and among randomized group included discectomy (n = 9 refused, n = 15 accepted), laminectomy (28/47), foraminotomy (24/40), fusion (10/11), and instrumentation (9/12). Long-term success rates at 2.9±1.1 years were SCS 9/19 (47%) vs. reoperation 3/26 (12%).	"[S]CS is more effective than reoperation as a treatment for persistent radicular pain after lumbosacral spine surgery, and in the great majority of patients, it obviates the need for reoperation."	Study tests SCS vs. re-operation, but does not document how it would compare with a quality functional restoration program. Re-operation may be critiqued for being analogous to "more of the same" that had previously failed, thus producing a potential bias in favor of the new treatment.
Kriek, 2016 **(score=6.5)**	Spinal Cord Stimulation	RCT, crossover study	Sponsored by St. Jude Medical. FH is a paid consultant for Grünenthal GmbH; DdR has a patent on burst stimulation and is a paid consultant for St. Jude Medical. The remaining authors declare no conflict of interest.	N=43 patients with complex regional pain syndrome.	Mean age: 42.55 years; 4 males, 25 females.	Standard (n=35) – patients received 40 Hz of stimulation in the CRPS-affected area. Vs 500 Hz (n=35) – patients received 500 Hz of stimulation in the CRPS-affected area. Vs 1200 Hz (n=35) – patients received 1200 Hz of stimulation in the CRPS-affected area.	At 3 months (10 week follow up period).	The VAS scores for the standard, 500 Hz, 1200 Hz, Burst, and Placebo groups were 39.83, 40.13, 42.89, 47.98, and 63.74, respectively. The overall statistical outcome was $F_{(1,4)}$=7.834; p<0.001. The McGill pain scores for average pain were 4.70, 5.10, 5.31, 5.66, 7.07, respectively the overall statistic outcome was $F_{(1,4)}$=11.370; p<0.001. For Minimal pain: 3.17, 3.57, 3.69, 4.31, 5.59, $F_{(1,4)}$=13.009; p<0.001. For maximum pain: 6.31, 6.86, 6.52, 7.28, 8.35, $F_{(1,4)}$=5.902; p<0.001. For Pain during exertion: 6.35, 6.66, 6.86, 7.35, 8.41, $F_{(1,4)}$=8.152; p<0.001. The	The results from this trial allow to conclude that stimulation with 40, 500, 1200 Hz and burst are equally effective in relieving neuropathic pain related to CRPS and are significantly better than placebo.	Crossover trial. Data suggest variation in patient preferences for various frequencies in SCS but suggest all stimulation settings improved compared with placebo/sham.

						Vs. Burst (n=35) – Patients received multiple burst complexes with an overall frequency of 40 Hz. Vs. Placebo (n=35) – patients received 100 Hz stimulus, however the IPG was switched off after "programming" the stimulus.		Global Perceived effect Scores are: Satisfaction: 5.28, 5.31, 4.97, 4.72, 3.52, $F_{(1,4)}$=58.081; p<0.001. Improvement: 4.93, 5.00, 4.72, 4.55, 3.79, $F_{(1,4)}$=4.795; p<0.001.		
Deer, 2017 (score= 4.5)	Spinal Cord Stimulation	RCT	Sponsored by Spinal Modulation, LLC and St. Jude Medical. Several authors had conflicts of interest.	N= 152 patients with chronic, intractable neuropathic pain of the lower limbs associated with a diagnosis of CRPS or causalgia.	Mean age: 52.5 years; 74 males, 78 females.	DRG (n=76) – patients received dorsal root stimulation. Vs SCS (n=76) – patients received spinal cord stimulation.	3 months, 6 months, 9 months, and 12 months.	At 3 months, 69 (DRG) and 70 (SCS) subjects met the composite end point of success, defined as ≥50% in pain reduction at both the trial phase and the indicated follow up without a stimulation-related neurological deficit in the modified intent-to-treat population, p<0.001. At 6 months: 69 (DRG) and 68 (SCS), p=0.04. At 9 months: 66 (DRG) and 65 (SCS), p=0.02. At 12 month: 66 (DRG) and 66 (SCS), p=0.005.	"In conclusion, CRPS I and causalgia, in their chronic forms, are difficult to treat with variable outcomes with conservative symptom management."	No sham/placebo control. Data suggest dorsal root ganglion stimulation may benefit some patients with CRPS who failed other treatments at up to 12 months.

Amputation has been used to treat CRPS [406-411] [220, 412-414].

Amputation for CRPS

Not Recommended.

Amputation is not recommended for treatment of CRPS.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**
Level of Confidence – Moderate

Rationale:	There are no quality studies of amputation. A comparative case series reported modest differences in pain (VAS 80 vs. 91) between an amputated group and non-amputated group [407]. Amputation has permanent adverse consequences, is high cost, does not have quality evidence of efficacy and is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Complex regional pain syndrome, reflex dystrophy syndrome, CRPS ,controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 323 articles in PubMed, 51 in Scopus, 45 in CINAHL, 45 in Cochrane Library, 70 in Google Scholar, and 31 from other sources. We considered for inclusion 128 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 31 from other sources. Of the 159 articles considered for inclusion, 64 randomized trials and 37 systematic studies met the inclusion criteria. There are no quality studies evaluating amputation for the treatment of CRPS.

Prognosis

The prognosis of CRPS ranges from excellent to guarded. The outcome is believed to be heavily dependent on the rate of, and compliance with functional restoration that primarily relies on strengthening and aerobic exercises. Fear avoidant belief training, cognitive behavioral therapy, multidisciplinary rehabilitation programs, selective medications, and other interventions all help produce better outcomes. Lack of focus on these interventions and lack of focus on active exercise worsens prognoses. Earlier use and earlier return to work all help improve outcomes. Earlier treatment with evidence-based approaches are also believed to improve outcomes.

Differential Diagnosis

The differential diagnosis of CRPS is diverse. Below are the more common alternate diagnoses, rather than a complete list.

- Diabetic neuropathy

- Alcoholic neuropathy
- Autoimmune neuropathies
- Rheumatological disorders
- Vasculitis
- Cerebrovascular accident
- Multiple sclerosis pain
- Peripheral nerve injuries
- Trauma
- Radiculopathy
- Radiculitis
- Herpes zoster/Shingles
- HIV/AIDS
- Guillain-Barre Syndrome
- Intracranial aneurysm
- CNS tumor
- Malingering
- Idiopathic

Complications / Comorbidities

- Diabetes mellitus
- Alcohol
- Autoimmune disorders
- Nutritional deficiencies
- Pernicious anemia
- Herpes zoster/shingles
- Diabetic neuropathy
- Rheumatological disorders
- Stroke
- Multiple sclerosis
- Peripheral nerve injuries
- Radiculopathy
- Radiculitis
- Herpes zoster/Shingles
- HIV/AIDS
- Hypothyroidism
- Nutritional deficiencies
- Intracranial aneurysm
- Advocagenic influences
- Idiopathic

Follow-up Care

It is **Recommended (I)** that patients with CRPS should have a follow-up visit every week by a nhealth care provider or while still out of work. Appointments throughout the treatment period should generally be time-contingent, i.e., scheduled as opposed to obtained secondary to changes in pain complaints and symptoms.

Initial visits should include initiating and an ongoing focus on function. These appointments should obtain more information from the patient, confirm the history information is consistent, observe for injury/illness behaviors, confirm the diagnosis, and assess the need for psychological referral and evaluation. These initial appointments for CRPS should institute progressive strengthening and aerobic exercises, select medications with demonstrated efficacy for CRPS treatment, include fear avoidance belief training, establish physical therapy care and pain psychological services if needed.

The educational process of informing the patient about functional status and the need to engage in a functional rehabilitation program focusing on restorative exercises should be reinforced. These restorative exercise program components should be labeled the cornerstone of the medical management plan for the patient's pain. The provider should take care to answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery.

Those patients requiring treatments in pain programs require more frequent follow-ups. Subsequent follow-up is **Recommended (I)** to be less frequent, and tailored to the patient's needs. In cases where the patient has returned to work, fully functional and on minimal or steady-state maintenance NSAID medications, follow-up every 6 to 12 months is **Recommended (I)**. However, in the active rehabilitation phase for patients with neuropathic pain, follow-ups weekly for as much as 2 or 3 months is **Recommended (I)** to also be conducted if there is need for physical therapy and occupational therapy to sustain a team-oriented focus on restoration and achievement of functional goals.

Job Analysis

The primary purpose of job analyses for patients with CRPS is to identify job tasks that the worker may be able to perform. The job analysis may also assist in identifying progressively more demanding or graded job tasks that the patient could be transitioned into as part of their functional restoration program.

Fibromyalgia

Summary of Recommendations

The following summary table contains recommendations for evaluating and managing fibromyalgia from the Evidence-based Chronic Pain Panel. These recommendations are based on critically appraised higher quality research evidence or, when such evidence was unavailable or inconsistent, on expert consensus as required in ACOEM's Methodology. Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient – Recommended (Consensus-based), "I" Level
- Insufficient – No Recommendation (Consensus-based), "I" Level
- Insufficient – Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

Cytokine Testing for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Antibodies for Fibromyalgia	Strongly Recommended, Evidence (A)
Non-specific Inflammatory Markers for Screening for Inflammatory Disorders for Fibromyalgia	Recommended, Evidence (C)
ANSAR Testing for Diagnosing Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Functional MRIs for Diagnosing Fibromyalgia	No Recommendation, Insufficient Evidence (I)
SPECT/PET for Diagnosing Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Needle EMG and Nerve Conduction Study to Diagnose Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Surface EMG for Diagnosing Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Local Anesthetic Injections for Diagnosing Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Functional Capacity Evaluations for Fibromyalgia	Recommended, Insufficient Evidence (I)
Bed Rest for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Fear Avoidance Belief Training for Fibromyalgia	Recommended, Insufficient Evidence (I)
Aerobic Exercise for Fibromyalgia	Strongly Recommended, Evidence (A)
Strengthening, Stabilization, and Resistance Exercise for Fibromyalgia	Moderately Recommended, Evidence (B)
Stretching Exercises For Fibromyalgia (Non-Yoga)	Not Recommended, Evidence (C)
Yoga for Fibromyalgia	Recommended, Insufficient Evidence (I)
Pilates for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Swimming for Fibromyalgia	Recommended, Evidence (C)
Aquatic Therapy for Fibromyalgia (Other than Swimming)	Moderately Recommended, Evidence (B)
Tai Chi for Fibromyalgia (Not Swimming)	Moderately Recommended, Evidence (B)
Spa and Balneotherapy for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Mirror Therapy for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Whole Body Vibration for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Oral NSAIDs for Fibromyalgia	Recommended, Evidence (C)

Acetaminophen for Treatment of Fibromyalgia	Recommended, Insufficient Evidence (I)
Norepinephrine Reuptake Inhibitor Anti-depressants (TCAs) for Fibromyalgia	*Amitriptyline:* Moderately Recommended, Evidence (B); *Dothiepin, Esreboxetine, Amitriptyline combined with Fluoxetine:* Recommended, Evidence (C)
Selective Serotonin Reuptake Inhibitors for Fibromyalgia	Moderately Recommended, Evidence (B)
Serotonin Norepinephrine Reuptake Inhibitors (e.g., Duloxetine, Milnacipran) for Fibromyalgia	Moderately Recommended, Evidence (B)
Noradrenergic and Specific Serotonergic Antidepressants for Fibromyalgia	Recommended, Evidence (C)
Serotonin Receptor Antagonists for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Bupropion, Trazodone, or Pramipexole for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Atypical Antipsychotics for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
NMDA Receptor Antagonists for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Anti-Convulsants for Fibromyalgia	Moderately Recommended, Evidence (B)
Glucocorticosteroids for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Dehydroepiandrosterone (DHEA) for Fibromyalgia	Not Recommended, Evidence (C)
Calcitonin for Fibromyalgia	Not Recommended, Evidence (C)
Vitamin D for Fibromyalgia	Recommended, Evidence (C)
Melatonin for Fibromyalgia	Recommended, Evidence (C)
Hormone Replacement Therapy for Fibromyalgia	Not Recommended, Evidence (C)
Raloxifen for Fibromyalgia	Not Recommended, Evidence (C)
Oxytocin for Fibromyalgia	Not Recommended, Evidence (C)
Growth Hormone for Fibromyalgia	Recommended, Evidence (C)
Pyridostigmine for Fibromyalgia	Not Recommended, Evidence (C)
Ritanserin for Fibromyalgia	Not Recommended, Evidence (C)
S-Adenosylmethionine for Fibromyalgia	Not Recommended, Evidence (C)
Creatine for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Terguride for Fibromyalgia	Not Recommended, Evidence (C)
Valcyclovir for Fibromyalgia	Not Recommended, Evidence (C)
Sodium Oxybate for Fibromyalgia	Moderately Recommended, Evidence (B)
Zolpidem for Fibromyalgia	Not Recommended, Evidence (C)
Coenzyme Q for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Acetyl 1-Carnitine for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Antidiencephalon for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Dolasetron for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Zopiclone for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Ondansetron for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Skeletal Muscle Relaxants for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Alpha1-Antitrypsin for Fibromyalgia	Not Recommended, Evidence (C)
Topical Medications and Lidocaine Patches for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Opioids for Fibromyalgia	*See Opioid Guideline.*
Kinesiotaping/Taping for Fibromyalgia	Not Recommended, Evidence (C)
Magnets/Magnetic Stimulation for Fibromyalgia	Not Recommended, Evidence (C)
Weight Reduction for Fibromyalgia	Recommended, Evidence (C)
Dietary Interventions for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Music Therapy for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Homeopathy for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Herbal, Alternative, Complementary or Other Preparations or Treatments for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Reiki for Fibromyalgia	Not Recommended, Evidence (C)
Qigong for Fibromyalgia	No Recommendation, Insufficient Evidence (I)

Acupuncture for Fibromyalgia	Recommended, Evidence (C)
Manipulation and Mobilization for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Massage for Fibromyalgia	Recommended, Insufficient Evidence (I)
Myofascial Release for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Reflexology for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Hot and Cold Therapies for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Hyperbaric Oxygen for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Interferential and Ultrasound for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Pulsed Electromagnetic Therapy for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Microcurrent Cranial Electrical Stimulation for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Cortical Electrostimulation for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Transcranial Direct Current Stimulation for Fibromyalgia	No Recommended, Insufficient Evidence (I)
Transcranial Magnetic Stimulation for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Low-Level Laser Therapy for Fibromyalgia	Not Recommended, Evidence (C)
Transcutaneous Electrical Nerve Stimulation (TENS) for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Other Electrical Therapies for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Iontophoresis for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Ganglion Blocks for Fibromyalgia	Moderately Not Recommended, Evidence (B)
Ketamine Infusions for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Lidocaine Infusions for Fibromyalgia	Not Recommended, Evidence (C)
C2 Nerve Stimulation for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Prolotherapy Injections for Fibromyalgia	Not Recommended, Insufficient Evidence (I)
Self-Management for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Body Awareness and Self-Awareness for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Attention Modification for Fibromyalgia	Not Recommended, Evidence (C)
Guided Imagery for Fibromyalgia	Not Recommended, Evidence (C)
Virtual Reality for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Mindfulness Intervention for Fibromyalgia	Recommended, Insufficient Evidence (I)
Acceptance and Commitment Training for Fibromyalgia	Recommended, Insufficient Evidence (I)
Psychoeducational Treatment for Fibromyalgia	Recommended, Insufficient Evidence (I)
Written Pain Education and Disclosures for Fibromyalgia	No Recommendation, Insufficient Evidence (I)
Shared Decision Making for Fibromyalgia	Recommended, Insufficient Evidence (I)
Psychological Treatment/Behavioral Therapy for Fibromyalgia	*See Behavioral module of Chronic Pain*
Rehabilitation for Delayed Recovery for Fibromyalgia	*See Behavioral module of Chronic Pain*
Biofeedback for Fibromyalgia	*See Behavioral module of Chronic Pain*
Relaxation & Meditation Training for Fibromyalgia	*See Behavioral module of Chronic Pain*
Functional Restoration for Fibromyalgia	*See Behavioral module of Chronic Pain*
Work Conditioning, Work Hardening, and Early Intervention Programs for Fibromyalgia	*See Behavioral module of Chronic Pain*
Interdisciplinary Pain Rehabilitation Programs for Fibromyalgia	*See Behavioral module of Chronic Pain*
Other “Ad Hoc” Functional Restoration for Fibromyalgia	*See Behavioral module of Chronic Pain*

Related Terms

Fibromyalgia syndrome
Fibrositis
Fibrositis syndrome
Chronic widespread pain

Introduction

Fibromyalgia is a chronic, anatomically widespread pain disorder of unknown etiology characterized by diffuse muscle pain often accompanied by fatigue, waking unrefreshed, and cognitive symptoms [415-417] [418]. It is thought to occur based primarily on abnormal central nervous system pain processing that mischaracterizes normal stimuli as unusually painful [419] [420] [421, 422] [423-436] [437] although some peripheral pain mechanisms are also theorized [418, 438].

Fibromyalgia is a unique disorder that has major psychological components (depression and other problems typically affecting more than half of patients). There are also strong tendencies towards *prior* psychiatric disorders that predate the onset of symptoms. The strongest tendency is for pre-existing depression, although it is not the only psychiatric diagnosis as others appear involved. Thus, evaluations for depression and other conditions are often needed. Additionally, there is evidence that patients with fibromyalgia respond to different therapies than do other patients with chronic pain.

Recent studies suggest fibromyalgia is not merely a pain disorder, as population-based studies reported more than twice risk of coronary heart disease among those with fibromyalgia [439, 440] and a 2.44-fold risk of motor vehicle crash [441].

As fibromyalgia is widely believed to primarily reside in the central nervous system, it is also considered non-occupational. While there is no quality evidence that fibromyalgia is work-related, this evidence-based guideline addresses the evaluation and treatment of patients with fibromyalgia because of the (i) prevalence of the condition, (ii) lack of widespread knowledge regarding evidence-based treatment approaches to manage this disorder, (iii) significant evidence-based differences in clinical management, and (iv) the insights that may be gained by comparing and contrasting these patients with others with chronic pain.

Treatment Overview

Evidence-based treatment of patients with fibromyalgia consists primarily of progressive aerobic exercises, potentially combined with strengthening exercises and anti-depressants. **Aerobic exercise is the most important exercise intervention and is typically introduced as a graded exercise intervention.** There is evidence that strengthening exercises are beneficial. Cognitive-behavioral psychotherapeutic interventions and physical therapy-based interventions to minimize the impact of fear avoidance beliefs ("kinesiophobia") are recommended. Fear avoidance belief training (FABT) appears required, as patients frequently believe that exercise is harmful [442]. FABT for fibromyalgia patients also potentially impacts on adherence to increasing occupational and non-occupational activities, as the main thrust of treatment is to maintain and increase activity, not decrease it through either self-limitations or prescribed restrictions.

Regardless of whether depression is present, anti-depressants are the first-line pharmaceutical treatment for fibromyalgia. This is the only major pain disorder for which selective serotonin reuptake inhibitor (SSRI) anti-depressants are effective, providing additional, robust evidence that this is a unique disorder that is distinguished from other chronic pain conditions. Both tricyclic anti-depressants and dual serotonin/norepinephrine reuptake inhibiting anti-depressants are also effective. Increased efficacy has been documented in combining a low-dose tricyclic anti-depressant with an SSRI. Treatment may also include NSAIDS. Studies also suggest modest benefits from gabapentin and pregabalin.

Risk and Causation

The prevalence of fibromyalgia has been estimated at 1-2%, or approximately 4 million US citizens [443] [444]. Increased risk of widespread pain and a prevalence of 4% with "fibromyalgia-like syndromes" has been reported after motor vehicle crash [445]. Numerous studies have reported increased risk among females [446], [447] [448] [443, 444] and those who are obese [447, 449], [450] [443]. A family history of fibromyalgia/widespread pain and genetics factors are also apparent risks [437, 446] [436, 451-453] [454].

There is no quality epidemiological evidence that fibromyalgia (or the closely related *chronic widespread pain*) are occupational conditions. There are no quality cohort or case-control studies. None of the few studies reported have adjusted for the major risk factors (see below). More disability has been reported in those with more physically demanding jobs [455] and one study reported more fibromyalgia among those with more demanding jobs. [456]

A longitudinal consecutive case series reported 23% of patients with chronic disabling occupational musculoskeletal disorders in a chronic pain program also met criteria for fibromyalgia; those with fibromyalgia had higher MMPI disability profiles with much lower return to work status at one year [457]. However, the data were not adjusted for most of the common, major fibromyalgia risk factors. A second longitudinal consecutive case series from the same clinic found no associations with chronic widespread pain and reduced return to work status [458]. One study found widespread hyperalgesia to pressure and cold in knee osteoarthrosis patients, suggesting altered nociceptive system processing [459], thus suggesting a potential association with reduced exercise or activity.

Rheumatological disorders are well reported risks for fibromyalgia, including rheumatoid arthritis [443, 448, 460-462], Sjogren's [463], systemic lupus erythematosus [464, 465] [448]. Among rheumatological disorders, worsening disease is associated with greater risk of developing fibromyalgia [461]. There is some evidence fibromyalgia is associated with inflammatory markers (aka biomarkers) including IL-1RA, IL-6 and IL-8 [466, 467] [468-471], as well as immune system reactions [472].

Psychiatric and mental health disorders are robust risks. These include depression ([473-480] [352, 444, 447-449, 461, 464, 475, 481-488], anxiety [489] [444, 448, 484, 486, 488-491], stress , social disadvantage [443, 444, 461, 492], social support [493], cognitive difficulties [461, 488], psychological distress [461, 494], phobias [481], catastrophizing [488, 491, 495], bipolar disorder [496] [443], somatoform pain disorder,[497], somatization [989, 1002], panic disorder,[477, 478] and familial mood disorder.[477] Elevated somatic symptoms scores [444, 498-500], psychological distress,[501], health anxiety[498] and cosmetic use [502] have been reported. Divorced or separated marital status is a reported risk as is smoking [443]. Rates of depression have been described to be as high as 86%.[478, 480] High rates of adverse life events and/or a family history of depression have also been reported.[479, 503, 504]

Childhood physical, sexual abuse and maltreatment are reportedly strong risk factors for development of somatic pain disorders including fibromyalgia [446, 505-507]. Adrenergic dysregulation is a reported risk [508].

Two large prospective studies found strong risks of widespread pain and fibromyalgia from nonrestorative sleep or sleep problems [509, 510] and other studies have also suggested sleep disturbance is a significant associated factor [511] [475] [494] [512]. Fatigue is frequently found[120, 513-515] and altered hypothalamic-pituitary-adrenal axis function has been reported.[516]

There are many other reported risks including hemochromatosis (Mohammad 13), chronic hepatitis C infection [517-520]), human T-cell lymphotropic virus type I infection [521], autoimmune thyroid disease [522], low vitamin D [449, 523], low cortisol levels [524], and epilepsy [525]. One large study also reported increased risks with myocardial infarction, heart disease, stroke, liver disease, kidney disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, asthma, and stomach ulcer [443].

There are many commonalities reported between fibromyalgia and other somatic syndromes including: Irritable bowel syndrome [448, 475, 477, 526-529], headaches [443, 448, 527] [986], chronic fatigue syndrome [448, 494, 527, 530] [531], temporomandibular disorders and orofacial pain [532], multiple chemical sensitivity,[533]. Risks as high as 20- to 30-fold have been reported with chronic fatigue syndrome. It also has been reported that patients with these somatic syndromes are *more* likely to be not working, suggesting a lack of improvement with work cessation.[513]

It is recommended that patients with fibromyalgia remain at full work duty to achieve optimum benefits and clinical outcomes [534]. Placing these patients on restricted or modified duty is believed to result in a substantially increased probability of the patient becoming partially or totally disabled. In situations where patients are placed on modified duty or self-reduce their activities, it is recommended that they gradually resume normal activities. When increasing his or her activity levels, frequent health care support and reinforcing to the patient that he or she is not injuring himself or herself is often required (see Fear Avoidant Belief Training).

Medical History and Physical Examination

History

Fibromyalgia involves long-standing, widespread pain that typically involves the entire body or multiple body segments (e.g., both upper extremities and torso). Symptoms are always present, but may wax and wane with seeming propensities towards exacerbations with perceived stresses. Poor sleep quality is a common symptom and may, in part be etiologic. Approximately one-third of patients with fibromyalgia also have migraines and the co-existence of fibromyalgia with irritable bowel syndrome[535] is reported to be as high as 70%, suggesting significant psychosocial components. Symptoms and signs of affective disorders, particularly depression, are common. Other risk factors and contributing factors are reviewed elsewhere (see Etiology and Work Relatedness).

Prior diagnostic research criteria required muscle tenderness (tender points) [536]. More recently, the criteria were changed to only require widespread pain due to reported: 1) lack of common performance of the tender points examination in clinical settings, and 2) improper performance of the tender points examination [415]. Regardless, tender points are a common finding among those with fibromyalgia.

Tender points are specific places on the body (18 sites) that are sensitive to touch in patients with fibromyalgia, although tenderness elsewhere is usual. The most common type of fibromyalgia occurs without any underlying disorder and is classified as primary. In a minority of patients, fibromyalgia occurs in the setting of other inflammatory rheumatological disorders, such as rheumatoid arthritis, and is sometimes classified as secondary.

Physical Examination

The physical examination of patients with primary fibromyalgia is noteworthy for a lack of completely objective findings, as tenderness on examination requires subjective interpretation.[537, 538] Those with secondary fibromyalgia may have prominent findings characteristic of a disorder (e.g., rheumatoid arthritis). A key aspect of the physical examination for fibromyalgia patients is the exclusion of other disorders [423] [539].

Prior physical examination emphases were placed on ascertaining tender points are sought at 18 sites defined by the 1990 American College of Rheumatology (ACR) criteria. While not necessary for ascertaining the presence of fibromyalgia, examination of these and other sites remain helpful. However, evidence also suggests patients tend to have tenderness at "sham" tender points.[540] Palpation of structures beyond the 18 standardized sites helps ascertain how widespread the tender points are. Muscular sites are recommended. While palpating muscles, there should be inclusion of palpation of boney structures, such as the lateral epicondyle, scapular spine, C7 spinous process, and lumbar spinous process. Fibromyalgia may be associated with allodynia and hyperalgesia. There may be some limitation on range of motion, but while active range of motion to an extreme may elicit or augment the patient's pain, the final extent of that range of motion is generally nearly or completely normal.

Diagnostic Criteria

There are no quality studies to support the routine use of any diagnostic testing for the evaluation of patients with fibromyalgia. There are selective circumstances where certain tests may be helpful in identifying an underlying condition, e.g. rheumatological disorders.

Cytokine testing has been used to evaluate patients with fibromyalgia [541] [467, 471, 542-546] [466].

Diagnostic criteria as developed by the ACR now consist of widespread pain. Previously, the criteria included both a history of widespread pain of at least 3 months duration and pain on palpation using 4kg of force on at least 11 of 18 specific tender points. Regardless, patients may have tender points anywhere in the musculature or over boney structures.

Table 10. Diagnostic Criteria for Non-red Flag Conditions*

Trigger Points/ Myofascial Pain (See Shoulder Disorders Guideline)	Non-radiating, usually unilateral pain most commonly periscapular (generally unilateral and in body part subjected to injury)	Muscle taut band or knot with referred pain on palpation Palpation reproduces patient pain Absence of widespread tender points	None Occasionally, rheumatological testing is helpful to demonstrate an alternative disorder
Fibromyalgia*	Widespread non-radiating pain often with prior or current depression, other affective disorders, and/or other psychological issues; fatigue often present	Absence of "objective" findings on exam other than tender points (at least 11 of 18 tender points, usually largely symmetrical) Tender point(s) in muscle which when compressed reproduces patient's pain	No inflammatory markers in blood studies; normal MRI, EMG, x-rays; generally no antecedent physical trauma

* Adapted from the 2010 Preliminary American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity

Probable Diagnosis	Criteria	Somatic symptoms that may be considered
Fibromyalgia (2010)	1. Widespread pain index ≥ 7 and symptom severity scale ≥ 5 or WPI 3–6 and SS scale score ≥ 9. 2. Symptoms have been present at a similar level for at least 3 months. 3. No other disorder that would otherwise explain the pain.	Muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Table 11. Guidelines for Modification of Work Activities and Disability Duration

DISORDER	ACTIVITY MODIFICATIONS AND ACCOMMODATION	RECOMMENDED TARGET FOR DISABILITY DURATION*	
		Modified Duty Available	Modified Duty Not Available
Fibromyalgia	Ideally, no limitations. May need graded increase in activity levels to regain normal function if previously, significantly debilitated.	Activity limitations should be avoided.	Activity limitations should be avoided.

Diagnostic Recommendations

Cytokine Testing

Not Recommended.

Cytokine testing is not recommended to assist in diagnosing fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: Some studies suggest some differences in cytokines among fibromyalgia patients [541] [542-544, 547-549], there are no quality studies suggesting cytokine testing is helpful for evaluation of fibromyalgia patients, especially for altering treatment or outcomes. There may be targeted examples where such testing is helpful, such as research labs. Cytokine testing is minimally invasive, has negligible adverse effects, is moderate to high cost depending on numbers of tests performed, has no quality evidence of efficacy and thus is not recommended for evaluation of fibromyalgia.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: cytokine testing, cytokines;

fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 23 articles in PubMed, 42 in Scopus, 11 in CINAHL, 18 in Cochrane Library, 12,400 in Google Scholar, and 0 from other sources. We considered for inclusion 7 from PubMed, 1 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 11 articles considered for inclusion, 7 diagnostic studies and 1 systematic studies met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. In addition, low-quality evidence is listed in Appendix 4.

Antibodies have been used for evaluation of fibromyalgia patients [550-554].

Antibodies

Strongly Recommended.

Antibodies are strongly recommended as a selective screen to confirm specific disorders (e.g., rheumatoid arthritis, lupus) among patients with fibromyalgia.

Strength of Evidence – **Strongly Recommended, Evidence (A)**

Level of Confidence – **High**

Indications:	Patients with fibromyalgia without prior diagnostic evaluations, or with incomplete evaluations who have symptoms suggestive of a systemic rheumatological disorder. Diagnostic testing should generally include sedimentation rate. Other tests may include rheumatoid factor [555-558], antinuclear antibody level [559], and others [541, 560]. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.
Benefits:	Diagnosing an unknown condition.
Harms:	Negligible
Frequency/Dose/Duration:	One or two evaluations. IgM may require only one evaluation/test. A second evaluation may be indicated when either there is a significant change in symptoms. A second test approximately 4-6 weeks later is also needed where the finding is IgG and there is a need to show at least 4-fold increased IgG to secure a diagnosis. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.
Rationale:	Elevated antibody levels are highly useful for confirming clinical impressions of rheumatic diseases. However, routine use of these tests may result in inaccurate diagnoses due to false positives especially if there is a low pre-test probability. Measurement of antibody levels is minimally invasive, unlikely to have substantial

adverse effects, and is low to moderately costly depending on the specific test ordered. They are recommended for focused testing of a few diagnostic considerations. However, ordering of a large, diverse array of antibody levels without diagnostically targeting a few specific disorders is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Antibodies; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 26 articles in PubMed, 26 in Scopus, 5 in CINAHL, 10 in Cochrane Library, 13,800 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 1 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 3 diagnostic studies and 0 systematic studies met the inclusion criteria. A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: rheumatoid Factor; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 12 articles in PubMed, 127 in Scopus, 14 in CINAHL, 4 in Cochrane Library, 23100 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 4 articles considered for inclusion, 3 diagnostic studies and 0 systematic studies met the inclusion criteria. There are moderate-quality studies included in this analysis. Low-quality evidence is listed in Appendix 4.

Inflammatory markers have been used for evaluation of fibromyalgia patients [561-563].

Non-specific Inflammatory Markers for Screening for Inflammatory Disorders

Recommended.

Erythrocyte sedimentation rate, CRP and other inflammatory markers are selectively recommended for screening for signs of systemic inflammation among those with fibromyalgia.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Indications: Patients with fibromyalgia without prior diagnostic evaluations, or with incomplete evaluations who have symptoms suggestive of a systemic rheumatological disorder. These tests particularly include erythrocyte sedimentation rate [466] and C-reactive protein.

Benefits: Diagnosing an unknown condition.

Harms: Negligible

Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated when either there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.
Rationale:	Erythrocyte sedimentation rate is the most commonly used systemic marker for non-specific, systemic inflammation and is elevated in numerous inflammatory conditions as well as with infectious diseases. C-reactive protein has been linked with an increased risk of coronary artery disease. However, it is also a non-specific marker for other inflammation. Other non-specific markers of inflammation include ferritin, and an elevated protein-albumin gap, however those two markers appear to have no known clinical roles. CRP and ESR measurements are minimally invasive, have low risk of adverse effects and are low cost. They are recommended as a reasonable screen for systemic inflammatory conditions especially in patients with fibromyalgia without clear definition of a diagnosis and/or with incomplete explanation of rheumatological symptoms. However, test results should be interpreted cautiously as the specificity is not high. The ordering of a large, diverse array of anti-inflammatory markers without targeting a few specific disorders diagnostically is not recommended, as it the utility of such wide batteries of tests is dubious.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: C-reactive proteins; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 5 articles in PubMed, 161 in Scopus, 7 in CINAHL, 10 in Cochrane Library, 6000 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 diagnostic studies and 0 systematic studies met the inclusion criteria. A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Erythrocyte Sedimentation Rate; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 11 articles in PubMed, 59 in Scopus, 3 in CINAHL, 0 in Cochrane Library, 4190 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 0 diagnostic studies and 0 systematic studies met the inclusion criteria. There are no quality studies evaluating the utility of C-Reactive protein, erythrocyte sedimentation rate, and other non-specific inflammatory markers for the diagnosis of patients with fibromyalgia. There is low quality evidence listed in Appendix 4.

ANSAR testing has been used for evaluation of fibromyalgia patients [564][565, 566][567].

ANSAR Testing for Diagnosing Fibromyalgia.

Not Recommended.

ANSAR testing is not recommended to assist in diagnosing fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale:	ANSAR has not been shown to alter the clinical management of patients with fibromyalgia. The value of identifying abnormalities in autonomic tone, if they exist, has not been demonstrated. The value of pharmacologically treating such abnormalities if they are clinically silent and manifested by positive test results has also not been identified. ANSAR is non-invasive, has minimal risk of adverse effects depending on the maneuvers performed, but is moderately costly. ANSAR is not recommended for evaluation of patients with fibromyalgia. There may be a very limited indication for those with autonomic neuropathy.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: ANSAR Testing, Autonomic Nervous System Testing; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 7 articles in PubMed, 33 in Scopus, 14 in CINAHL, 3 in Cochrane Library, 12,900 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 2 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 8 articles considered for inclusion, 5 diagnostic studies and 0 systematic studies met the inclusion criteria. There are no quality studies evaluating ANSAR for the diagnosis of patients with fibromyalgia. There is low-quality evidence listed in Appendix 4.

Functional MRI has been used for research investigations of patients with fibromyalgia [568-574]. MRI has also been used in these patients [575].

Functional MRIs for Diagnosing Fibromyalgia

No Recommendation.

There is no recommendation for functional MRIs for diagnosing fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Two moderate quality studies suggested some cortical changes on fMRI in fibromyalgia patients [576, 577]. Thus, although there are research studies with suggested changes, there are no quality studies indicating that the findings on fMRIs are of sufficient sensitivity and specificity to permit identification of the presence or absence of fibromyalgia or to materially alter the clinical course. The clinical applications of the test have not been defined. Functional MRI is minimally invasive and has low adverse effects, is high cost, has some evidence of showing differences in fibromyalgia patients but no quality evidence suggesting it effects the clinical course and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: functional magnetic resonance imaging, fMRI; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 21 articles in PubMed, 62 in Scopus, 5 in CINAHL, 21 in Cochrane Library, 10,800 in Google Scholar, and 0 from other sources. We considered for inclusion 2 from PubMed, 0 from Scopus, 4 from CINAHL, 1 from Cochrane Library, 2 from Google Scholar, and 0 from other sources. Of the 9 articles considered for inclusion, 3 diagnostic studies and 0 systematic studies met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence is listed in Appendix 4.

SPECT has been used for evaluation of fibromyalgia patients [578-581].

SPECT/PET for Diagnosing Fibromyalgia

Not Recommended.

SPECT is not recommended to evaluate patients with fibromyalgia (aside from use in cases of suspected inflammatory arthropathies not diagnosed by more common tests). The use of PET scanning is also not recommended to evaluate patients with fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: One moderate quality study suggest SPECT was helpful in predicting ketamine response in hyperalgesic fibromyalgia patients [582]. SPECT and PET scanning of the brain may be of use in assessing the status of cerebrovascular perfusion, tumors, and neurodegenerative conditions, but aside from providing information of interest for research, these techniques have not been shown to be useful in influencing the management of patients with fibromyalgia. SPECT scanning may be useful in detecting inflammatory disease in the spine and other areas that might not be amenable to evaluation by other studies. SPECT and PET scanning are minimally invasive, have negligible adverse effects,

are high cost, have no quality evidence of efficacy for diagnosis of fibromyalgia, and so are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: SPECT, Single-Photon Emission Computed Tomography, Single Photon Emission Computed Tomography; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 9 articles in PubMed, 10 in Scopus, 0 in CINAHL, 2 in Cochrane Library, 4,030 in Google Scholar, and 0 from other sources. We considered for inclusion 4 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 0 from other sources. Of the 5 articles considered for inclusion, 2 diagnostic studies and 0 systematic studies met the inclusion criteria. A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: PET, PET Scans, Positron Emission Tomography; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 2 articles in PubMed, 0 in Scopus, 40 in CINAHL, 0 in Cochrane Library, 0 in Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria. There is a moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Electrodiagnostic studies have been used for evaluation of fibromyalgia patients [583].

Needle EMG and Nerve Conduction Study to Diagnose Fibromyalgia

Not Recommended.

Needle EMG and nerve conduction studies are not recommended for evaluation of fibromyalgia patients.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: EMG/NCS is often helpful for helping define the location and extent of neurological impairments (e.g., see Low Back Disorders, Cervical and Thoracic Spine Disorders and Hand, Wrist and Forearm Disorders Guidelines). EMG/NCS is minimally invasive, has minimal adverse effects, is moderately costly, has not been found to be diagnostically helpful outside of the evaluation of symptoms consistent with neurological impingement, and is thus is not recommended for routine diagnosis in fibromyalgia patients.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date

limits using the following terms: Electrodiagnosis, Electrodiagnostic, Electrodiagnostic Studies; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 56 articles in PubMed, 15 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 0 in Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria. There are no quality studies evaluating the use of Needle EMG and/or Nerve Conduction Studies to diagnose fibromyalgia.

Surface EMG has been used for evaluation of fibromyalgia patients [584, 585] [586-588].

Surface EMG for Diagnosing Fibromyalgia.

Not Recommended.

Surface EMG is not recommended for evaluation of fibromyalgia. There are selective indications for use with biofeedback.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Rationale: Surface EMG has no demonstrated value in the clinical evaluation or treatment of fibromyalgia with resultant altered management or improved clinical outcomes. Surface EMG may be of use in biofeedback training, and gait analysis for musculoskeletal and/or neurologic disorders, but it has no established use in the management of fibromyalgia and is thus not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Surface EMG, Surface Electomyography; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 25 articles in PubMed, 5 in Scopus, 3 in CINAHL, 0 in Cochrane Library, 3,310 in Google Scholar, and 0 from other sources. We considered for inclusion 4 from PubMed, 1 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 7 articles considered for inclusion, 3 diagnostic studies and 0 systematic studies met the inclusion criteria. There are no quality studies evaluating sEMG for the diagnosis of patients with fibromyalgia. There is low-quality evidence listed in Appendix 4.

Local Anesthetic Injections for Diagnosing Fibromyalgia

Not Recommended.

Local anesthetic injections are not recommended for diagnosing fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Harms:	See Table 12.
Rationale:	There are no quality studies demonstrating clinical utility of injections for diagnosis and evaluation of fibromyalgia. These injections are invasive, have adverse effects, are moderate to high cost and without evidence of efficacy are not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Local Anesthetic Injection; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 6 articles in PubMed, 16 in Scopus, 0 in CINAHL, 10 in Cochrane Library, 6440 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria. There are no quality studies evaluating local anesthetic injections for the diagnosis of patients with fibromyalgia.

Table 12. Adverse Effects of Injections

General complications of neuraxial injections, and of injections near the paravertebral muscles	Infection at site and remote (meningitis found in one German study following trigger point, facet, and epidural injections). Bleeding, including hematoma causing nerve compromise. Direct trauma to nerve, causing permanent damage or increased pain. Injection into the wrong space (artery, vein, inadvertent intrathecal, or thoracic cavity). This can lead to respiratory compromise, cardiac arrest, or pneumothorax.
Complications specifically related to the substance and amount injected (in addition to possible anaphylaxis)	Local anesthetics – seizures, cardiac collapse. Sympatholytics – hypotension, tachycardia, cardiac dysrhythmias. Corticosteroids* – endocrine dysfunction, diabetes, hypertension, dysphoria, immune compromise, phlebitis, muscle pain, osteoporosis, dependency, rarely nerve damage, etc. Baclofen* – anxiety, blurred vision, ataxia, coma, depression, dizziness, dysarthria, dystonic reaction, hallucinations, headache, respiratory depression, seizures, stroke, etc. Botulinum toxins – weakness, paralysis, respiratory compromise, diplopia, dizziness, injection site reaction.

*These adverse effects are mostly temporary aggravations and dependent on dose and frequency.

Functional Capacity Evaluations for Fibromyalgia

Recommended.

Functional capacity evaluations (FCEs) are recommended for evaluating select patients with fibromyalgia to attempt to objectify worker capability compared with either specific job or general job requirements.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications:	Need to objectify worker capabilities compared with either job specific or general job requirements. Should generally be performed only after treatment options have been utilized, implemented, and stability has been reached with apparent residual deficits. As complete functional recovery is normal for fibromyalgia where patients are compliant with aerobic and strengthening exercises, there is quite limited need for FCEs in these patients that is typically limited to those with co-morbid conditions such as rheumatoid arthritis with joint deformities.
Benefits:	Assess functional abilities and may facilitate greater confidence in return to work.
Harms:	Medicalization, transient worsening of pain with testing. Functional testing is performance-based, so patients may self-limit due to pain or fear of pain, and results may reflect minimal tolerable abilities rather than maximum physiological capacity. Understating capabilities may further medicalize and institutionalize impairments to the fibromyalgia patient's detriment.
Frequency/Dose/Duration:	Generally only once unless there is significant passage of time or apparent change in function.
Rationale:	FCEs are one of the few means to attempt to objectify limitations and are frequently used in the workers' compensation system. Because there are issues with suboptimal efforts that are not necessarily captured, they should be considered as one set of data about what a patient was willing to do on a given day. They should not be used to override the judgment about the work ability of a patient. They particularly should not be viewed as providing objective evidence when there is other corroborating evidence of subjective-objective mismatches or evidence the patient is able to accomplish more than was demonstrated at the time of the FCE. Fibromyalgia patients are particularly prone to these problems with FCEs [589] [590]. Most patients will not require an FCE, particularly where the patient is able to articulate a desire to return to work, along with stated capabilities that appear to match the clinical impression. An FCE may be helpful in identifying capabilities at an end of healing for purposes of attempting to support work limitations that are used to assign "permanent" restrictions and disability applications. However, providers should be

particularly aware of major secondary gain issues when FCEs are performed for these purposes and be particularly vigilant about test-retest reliability, test validity measures, and the need to unequivocally report all measures as well as any evidence of subjective-objective mismatches.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: functional capacity evaluation, FCE; fibromyalgia; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 3 articles in PubMed, 14 in Scopus, 0 in CINAHL, 8 in Cochrane Library, 15,400 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 2 articles considered for inclusion, 1 diagnostic study and 0 systematic studies met the inclusion criteria. There are no quality studies of the reliability and validity of FCEs for evaluating patients with fibromyalgia. There is low-quality evidence listed in Appendix 4.

F-Wave for Diagnosing Fibromyalgia

No Recommendation.

There is no recommendation for F-Wave for evaluating patients with fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Evidence: There are no quality studies of the reliability and validity of F-Wave for evaluating patients with fibromyalgia. There is low-quality evidence listed in Appendix 4.

Diagnostic Evidence Tables

Evidence for Cytokine Testing

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Wallace 2015 (5.5)	Cytokine testing	Diagnostic	No mention of COI or sponsorship.	N = 427 with FM for at least 1 year.	Aged 18 – 92 years, 379 females and 48 males.	Fibromyalgia (FM) Systemic lupus Erythematosus (SLE) Rheumatoid arthritis (RA).	FM (N = 160) vs RA (N = 98) vs SLE (N = 100). Controls (N = 119).	93 % sensitive and 89.4 % specific for the diagnosis of FM vs 119 controls. Cytokine/ chemokine composite test scores were 33.7 and 19 on a scale of 100. FM patients showed the lowest levels of IL-6 compared to RA, SLE patients and controls—which were within 2 % of each other, ($p < 0.00001$).	"This assay can be a useful tool in assisting clinicians in differentiating systemic inflammatory autoimmune processes from FM and its related syndromes and healthy individuals."	Data suggest FM patients have distinctive patterns of Cytokines and chemokine profess useful in distinguishing between FM and other inflammatory and/or autoimmune diseases.
Deitos 2015 (4.5)	Cytokine testing	Diagnostic	Sponsored by the following Brazilian funding agencies: National Council for Scientific and	N = 177 with Central sensitivity syndrome (CSS).	Aged CSS / CSS without persistent pain / and controls: 49.63±15.51 / 43.63±11.04	(VAS) ≥ 40mm >3 months associated with functional disability	CSS with persistent somatic/visceral nociception: Osteoarthritis (N = 27) And Endometriosis (N = 32). CSS	12.9% at stage I, 22.6% at stage II, 41.9% at III, and 22.6% at IV. Pain and severity of depressive	"Neuroplasticity mediators could play a role as screening tools for pain clinicians, and as validation of	Data suggest neuroplasticity mediation may be of chemical use for screening patients with CSS.

			Technological Development-CNPq, ILST, W.C., J.A.D.-S., GPPG of Hospital de Clınicas de Porto Alegre, Porto Alegre, W.C.—Grant #100196, Coordination for the Improvement of Higher Education Personnel-CAPES, A.D., L.M., A.d.S., the International Cooperation Program-CAPES (023/11), FIPE/ HCPA, Porto Alegre, Rio Grande do Sul, Brazil, FINEP, Grant number - 1245/13. No COI.		/ and 45.84±11.97 .		without persistent somatic/visceral nociception: Fibromyalgia (N = 22) and Myofascial Pain Syndrome (N = 29) and Chronic Tension Type Headaches (N = 30). Pain free controls (N = 37).	symptoms; TNF-a, IL10, or IL6; correlated to BDNF (Spearman r = 0.38, p < 0.001 for pain; Spearman r = 0.41, p < 0.001 for severity of depression symptoms.	the complex and diffuse symptoms of these patients.”	

Ross 2010 [4.5]	Cytokine testing	Diagnostic	Each author has been sponsored by either one or more of the following grants: Post-doctoral Fellowship Award from the National Institutes of Health and is a Sub-Investigator on pharmaceutical clinical trials with Schwarz Biosciences, Jazz Pharmaceuticals, and Pfizer, Incorporated, the Fibromyalgia Information Foundation.	N = 24 with FM.	Aged 28 – 60 years, 19 females and 5 males.	FM	With normal growth hormone or GH (N = 12) Vs Without normal GH (N = 12)	Hypothalamic-pituitary-hormonal axes (HPHA) dysfunction associated with FIQ VAS, increased number of tender-points and higher cumulative myalgic scores, a higher BMI and an increased percentage of body fat, (p = 0.047). The workload achieved during the treadmill test in GH nonresponders vs responders, (p = 0.001) and after controlling for workload (p < 0.001) percentage of body fat, (p = 0.001) and both simultaneously, (p = 0.006). % of body fat did not influence the observed group differences in	"The results reported herein suggest that a defective growth hormone response to exercise may be associated with increased levels of blood cytokines and pain severity in FM."	Data suggest that a dysfunctional growth hormone (GH) response to exercise may be associated with increased levels of b loo cytokines and severity of pain in FM patients.

								IL1-α (p = 0.034), IL-6 (p = 0.021) nor IL-8 (p = 0.006).		
Blanco 2010 [4.0]	Cytokine testing	Diagnostic	Sponsored by the Spanish National Health Institute Carlos III, the Biohealth Research Office [OIB] of the Principado de Asturias, Spain (IB and VC), and by the Crafoords and Lundström Foundations (SJ). No COI.	N = 138 with Fibromyalgia syndrome (FMS).	Mean age 53.0 (8.4) / 54.5 (8.0) in FMS and GP group, 138 females.	FMS	Fibromyalgia syndrome or FMS (N = 79) and General population or GP (N = 59).	Those with normal MM [n=82 (59.4%)] and with MS, MZ, SZ / and with ZZ AATD genotypes [n=56 (40.6%)]. Plasma levels of MCP-1, VEGF, and TNFα were lower in AATD subjects with FMS than in those without FMS (p = 0.000, 0.000, and 0.046). Plasma MCP-1 cutoff value of ≤130 pg/ml,	"[A]ATD seems to play a critical role in FMS development and maintenance in at least a subgroup of FMS patients with this inherited disorder due to mechanisms to be yet discovered."	Data suggest AATD plays a role in some FM patients but the etiology of this is unknown.

								FMS and GP with a sensitivity of about 93% and a specificity of 79%.		

Evidence for Antibodies

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Werle, 2001 (4.5)	Antibodies	Diagnostic	Sponsored by a grant from the German Federal Health Ministry. No mention of COI.	N = 269 patients, 203 patients with Fibromyalgia (FM) and 64 pain free control subjects.	Mean age: 52 Sex(M:F) 16:187	Fibromyalgia	Prevalence of autoantibodies against serotonin, thromboplastin, and ganglioside Gm1 in patients diagnosed with FM and control patients.	In patients with FM the prevalence of autoantibodies against serotonin was significantly higher than controls (20% vs 5% (p = 0.003)). Antibodies against thromboplastin were more prevalent in FM patients than in controls (43% vs 9% (p < 0.001).	"There is an elevated prevalence of antibodies against serotonin and thromboplastin in patients with FM. The pathophysiological significance of this finding is unknown."	Data suggests FM patients have elevated numbers of antibodies against serotonin and thromboplastin.

Evidence for Rheumatoid Factor

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Silveira, 2007 (5.5)	Rheumatoid Factor	Study type: Diagnostic	Conflict of Interest: No mention of Sponsorship or COI.	Sample size: N = 768 patients.	Age/Sex: Mean age: 52 Sex(M:F) 163:605	Rheumatoid Factor	Anti- Cyclic Citrullinated Peptides (CCPs)	Positive predictive value of anti-CCP antibodies and Rheumatoid Factor (RF) were 79% and 56% (p<0.001) respectively. The likelihood ratio was 17.9 for anti-CCP and 6.2 for RF (p<0.001).	"In the population tested for RF, anti-CCP is more useful test than RF to help for the diagnosis of RA."	Data suggests anti-CCP has better specificity for detecting RA than RF
Serdaoglu, 2007 (5.0)	Rheumatoid Factor	Diagnostic	No mention of sponsorship or COI.	N = 78 patients with fibromyalgia or Rheumatoid Arthritis.	Mean age: 48.3 ± 12.8 Sex(M:F) 0:40	Rheumatoid Factor	Anti- Cyclic Citrullinated Peptides (CCPs)	In patients tested for anti-CCP, those who test negative (N=20) 18 had RF. In comparison, those who test anti-ccp positive (N=20) only 8 had RF (p<0.05)).	"In conclusion, early development of erosive disease in RA is associated with the presence of several autoantibodies and the IgM RF is still mostly used as a screening marker in the	Data suggests anti-CCP antibodies have comparable sensitivity to IgMRF in the diagnosis of RA but with much higher specificity.

								A significant correlation was found between anti-CCP and RF (r=0.03, (p=0.02)).	diagnosis of RA."	
Wolfe, 1991 (5.0)	Rheumatoid Factor	Diagnostic	Supported by National Institutes of Arthritis. No mention of COI.	N = 8,287 patients with Rheumatoid Arthritis (RA) or Inflammatory Rheumatic disorders (IRD) or noninflammatory rheumatic (NIRD) disorders.	Mean age: RA group 55.3, IRD patients 45.6, and NIRD patients 53.3. Sex(M:F) 2463:5824	Rheumatoid Factor	Latex Fixation	Latex fixation had a sensitivity of 81.6% for rheumatoid factor testing. Latex fixation had a specificity against NIRD of 96.6% and 95.2% against IRD.	"This study suggests that latex testing is far more specific than has been believed and that the titer is not spuriously increased with age."	Data suggests latex testing to be specific for diagnosing RA and is not spuriously affected by age.

Evidence for Functional MRIs

Author Year Score	*Category*	*Study type*	*Conflict of Interest*	*Number*	*Age/Sex*	*Area*	*Diagnoses:*	*CT used no*	*MRI used*	*T1 weighted images*	*T2 weighted images*	*X-ray no*	*Myelography*	*More than one rater*	*Surgery Performed*	*Clinical Outcomes*	*Long-term Follow-up (mean*	*Results*	*Conclusion*	*Comments*
Gracely 2002 (4.0)	*fMRI*	*Diagnostic*	*Supported by National Fibromyalgia Research Association. No*	*32 patients consisting of 16 patients*	*Mean age of FM group 52.6, HC group 45.8.*	*Entire brain.*	*FM*	*No*	*1.5 Tesla vision system*	*Yes*	*No*	*No*	*No*	*No*	*No*	*No*	*No*	FM patients displayed significantly lower pressure pain thresholds (Mean±SEM) at the left	"The fact that comparable subjectively painful conditions	*Data suggest fibromyalgia in characterized by cortical or subcortical*

			mention of COI.	*diagnosed with FM, and 16 healthy controls (HC).*	*Sex(M:F) 2:30*													thumbnail compared with those displayed by control subjects. (1.4 ± 0.028 vs. 2.7 ± 0.23 kg/cm² (p < 0.001)) Similar pain in both groups resulted in 19 regions of increased regional cerebral blood flow in healthy controls and 12 significant regions in patients.	resulted in activation patterns that were similar in patients and controls, whereas similar pressures resulted in no common regions of activation and greater effects in patients, supports the hypothesis that FM is characterized by cortical or subcortical augmentation of pain processing. ”	*augmentation of pain processing.*
Lopez – Sola 2014 (4.0)	*Fibromyalgia*	*Diagnostic*	*Supported in part by the Ministry of Science and Innovation*	*N = 60 patients, consisting 35 patients with FM and 25 health*	*Mean age of FM group 46.55. HC group 44.64.*	*Whole Brain*	*FM*	*No*	*Achieva 3.0 TX system*	*No*	*No*	*No*	*No*	*No*	*No*	*No*	*No*	Compared with healthy controls, the FM group showed reduced task-related activation in primary/secondary	“FM patients showed strong attenuation of brain responses to nonpainful	*Data suggest fMRI is a reasonable tool to assess neural mechanisms involved in the*

			of Spain. No mention of COI.	*y control s (HC).*	*Sex(M :F) 0:60*												auditory cortices, middle temporal gyri, hippocampi, ventral basal ganglia, and inferior occipital gyri extending to the bilateral cerebellum. In FM patients, higher total FIQ and spontaneous pain scores were significantly correlated with lower activation magnitudes in visual areas. (P<0.05)	events in early sensory cortices, accompanied by an amplified response at later stages of sensory integration in the insula. These abnormalities are associated with core FM symptoms, suggesting that they may be part of the pathophysiology of the disease."	*pathophysiology of fibromyalgia.*

Evidence for SPECT/PET

Author Year (Score):	Study type:	Sample size:	Age/Sex:	Area of head:	Diagnoses:	SPECT or SPET:	MRI or CT:	More than one rater:	Surgery Performed:	Clinical outcomes assessed:	Long term follow-up: (mean when noted)	Results:	Conclusion	Comments:
Geudj 2007 (4.0)	*Prospective/Diagnostic*	*N=17with FM. N=10 women w/out FM*	*0 males, 17 females; Mean age for FM 48±11. Control age is 52±7*	*Used to analyze blood flow in the global cerebrum.*	*Patients met the 1990 American College of Rheumatology criteria for Fibromyalgia.*	*SPECT*	*No*	*No*	*No*	*Yes*	*No*	*Comparison between responding and non-responding group showed a significant decrease in mediofrontal regional Cerebral Blood Flow (rCBF)) (k=292, T-Score=3.71, p-voxel<0.005). More extensive hypoperfusion of bilateral mediofrontal cortex in on-responders (k=1,371, T-score=6.12, p-voxel=0.00*	*"This prospective study showed that brain perfusion SPECT may predict response to ketamine in hyperalgesic FM patients. Larger studies and follow-up data, however, will be necessary to determine the long-term predictive value of*	*Data suggest SPECT may help to predict ketamine response in hyperalgesic fibromyalgia patients.*

												1) Cluster of hypoperfusion had a positive predictive value (PPV) of 100% and negative predictive value (NPV) of 91% for evaluating patients who respond to ketamine.	*these results.*	

Treatment Recommendations

Activity Modification

Fibromyalgia patients are believed to be particularly prone towards worsened clinical outcomes when occupational and non-occupational activities are limited [534]. Thus, activity limitations are not recommended and resuming normal activities is strongly recommended.

Bed Rest for Fibromyalgia

Not Recommended.

Bed rest is not recommended for fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Rationale:

There is no evidence that bed rest is helpful for fibromyalgia and it has been found to be unhelpful for LBP and other conditions. While bed rest has been used to treat fibromyalgia patients, it is believed to be strongly contraindicated and there are no quality studies evaluating its use as a treatment strategy. Bedrest, while non-invasive is costly (due to lost time) and can have documented adverse effects beyond those associated with deconditioning such as pulmonary emboli (1008). Bed rest is also thought to be strongly contraindicated as patients with fibromyalgia are known to benefit from exercise rather than sedentary activities or bedrest. Bed rest, therefore is not recommended for fibromyalgia.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is no quality evidence for the treatment of fibromyalgia with bed rest.

Fear avoidance belief training is a frequent component of the treatment of fibromyalgia [442].

Fear Avoidance Belief Training for Fibromyalgia

Recommended.

Inclusion of fear avoidance belief training during the course of treatment is recommended for treatment of fibromyalgia.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Indications:	All fibromyalgia patients, especially with vocalized FABs, and likely all fibromyalgia patients.
Benefits:	Faster return to normal activities
Harms:	Negligible
Frequency/Dose/Duration	Variable as needed
Indications for Discontinuation:	Resolution of FABs.
Rationale:	There are no quality trials of fear avoidance belief training. One post hoc analysis of a moderate quality trial found better results among those with reduced fear avoidance beliefs ("kinesiophobia"). One study documented that patients expected stress management to be efficacious (82%), while 50% felt aerobic exercise would be beneficial, and 30% felt aerobic exercise would worsen symptoms.[591] The patients mostly desired usual care and felt it would be beneficial (70%). Yet, the aerobic exercise group experienced the greatest benefits compared to the other treatments. As the evidence supporting exercise for fibromyalgia is strong, this suggests that fear avoidance beliefs ("kinesiophobia") are prevalent in these patients. These beliefs may also require additional supervised appointments to encourage and demonstrate the efficacy of exercise prior to transitioning to a home-based program. Fear avoidance belief training is not invasive, has negligible adverse effects, is low cost, is believed to be important in managing these patients and inclusion of these principles in the course of exercise training or supervision is thus recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other

sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Exercise

Exercise has been used to treat fibromyalgia and its efficacy has been evaluated in numerous RCTs. However, the majority of studies combined different exercises. Others left exercise programmatic components unstructured and/or did not clearly describe the interventions. These limitations restrict the utilization of a substantial body of the literature for purposes of drawing evidence-based conclusions regarding any single intervention. However, there is a considerable, remaining body of evidence to draw evidence-based conclusions on the relative value of aerobic, stretching, and strengthening exercises. Some evidence suggests exercise reduces inflammatory biomarkes [466]. Despite wide agreement on efficacy of exercise for fibromyalgia, only 47% of patients have been advised of exercise in one report [592].

Aerobic exercise has been used for treatment of fibromyalgia [593, 594] [1009-1012] [595] [596] [597] [598, 599] [600, 601] [602, 603] [604-606] [607-614] [597, 615, 616] [617] [618] [619, 620][621][622][623] [624-627] [628].

Aerobic Exercise for Fibromyalgia

Strongly Recommended.

Aerobic exercise is highly recommended for treatment of fibromyalgia

Strength of Evidence – **Strongly Recommended, Evidence (A)**

Level of Confidence – **High**

Indications:	All fibromyalgia patients. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's *Guidelines for Exercise Testing and Prescription,* 9th ed.,[161] in regards to health screening and risk stratification.
Benefits:	Improved pain, function, and endurance.
Harms:	Negligible. Vocalized pain worsening when beginning aerobic exercise is common in fibromyalgia patients, but mandatory to work through to experience meaningful functional gains. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Intolerance of weight bearing in severe lower extremity osteoarthrosis. Other musculoskeletal disorders possible (e.g., plantar heel pain).

Frequency/Dose/Duration:	A structured, progressive walking program at least 60-120 minutes per week, targeting at least 60-85% of predicted maximum heart rate [608]. One study suggested better results with greater numbers of steps taken per day [629]. Stationary exercise cycles and bicycling are generally not thought to be as helpful due to static use of the torso, although are superior to inactivity. The activity that the patient will adhere to is believed to be the one most likely to be effective, given that compliance is a recognized problem. Patients should be encouraged to maintain aerobic exercises on a long-term basis for preventive health consideration. Typically initiated with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Transition to home exercise program.
Indications for Discontinuation:	Aerobic exercise should not be abandoned in these patients, excepting short term for myocardial infarction, etc. Supervised exercise may be considered for discontinuation based on non-compliance, failure to progress, development of another disorder, or reaching a 4 to 6 week timeframe.
Rationale:	In all quality studies identified, aerobic exercise has been shown to be beneficial for treating fibromyalgia patients.[629-635]. Most but not all studies have suggested aerobic exercise was comparable to strengthening exercises [593, 636], and superior to flexibility/stretching exercises.[637-639] The available studies suggest better results with more intense aerobic exercise programs. Combinations of exercises has been found superior to individual types of exercise in one study [604]. One study also found superiority of belly dancing classes 1hr, twice a week for 16 weeks [640]. These findings indicate the primacy of aerobic exercises for treatment of fibromyalgia, likely supplemented by strengthening exercises. Aerobic exercise is not invasive, has negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, has strong benefits and thus is highly recommended. Patients need to be transitioned to a sustainable, home-based program.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated in this analysis. There is low-quality evidence listed in Appendix 4.

Strengthening, stabilization and resistance exercises have been used to treat fibromyalgia [641, 642][1016][643-648][649-653][598, 654, 655]

Strengthening, Stabilization, and Resistance Exercise for Fibromyalgia

Recommended.

Strengthening stabilization, and resistance exercise is moderately recommended for treatment of fibromyalgia.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Indications:	All fibromyalgia patients. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's *Guidelines for Exercise Testing and Prescription,* 9th ed.,[161] in regards to health screening and risk stratification.
Benefits:	Improved function, strength, and endurance. Improved ability to perform strength-demanding job tasks
Harms:	Negligible. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Other musculoskeletal disorders possible (e.g., strain).
Frequency/Dose/Duration:	Typically start with 3 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Supervised treatment frequency and duration is dependent on symptom severity and acuity and the presence of comorbid conditions. Transition to including home exercises.
Indications for Discontinuation:	Non-tolerance, failure to progress, development of another disorder (e.g., strain), or reaching a 4 to 6 week timeframe.
Rationale:	There is some quality evidence that strengthening exercise is helpful for treatment of fibromyalgia, with two studies having suggested benefits of strengthening exercises as compared to either flexibility exercises[656] or no exercise.[646] Strengthening exercises have also have found to be comparable to aerorobic exercises in most studies. [593, 636] Strength and function improved in another trial [657]. Resistance exercise has been found superior to relaxation [655]. Balance training has also been shown to have benefits compared with flexibility [653]. Strengthening, stabilization, and resistance exercises are not invasive, have negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, have strong rationale for indications, and thus are recommended. As evidence suggests superiority of aerobic exercise, strengthening exercises should be adjunctive to aerobic exercise.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence is listed in Appendix 4.

Stretching and flexibility exercises have been used to treat fibromyalgia [637-639, 653].

Stretching Exercises For Fibromyalgia (Non-Yoga)

Not Recommended.

Stretching and flexibility exercise is not recommended for treatment of fibromyalgia in the absence of functional deficits.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There is no quality evidence that stretching exercise are helpful for treatment of fibromyalgia despite widespread use. Stretching and flexibility exercises have been found to be inferior to aerobic exercise [1013-1015][607] and other trials have reported stretching exercises were inferior to strengthening exercises [656], Tai Chi [658], and balance training [653]. Thus, there are no trials suggesting flexibility exercises have utility in treating fibromyalgia patients. Additionally, stretching exercises are often used in combination with aerobic and strengthening exercises, from which a patients commonly then select only stretching as a surrogate for exercise compliance; in the case of fibromyalgia, data indicate this substitution would result in lack of progress. Stretching exercises are not invasive, have no adverse effects, are moderate cost in aggregate, have evidence of inefficacy and thus are not recommended.

There may be select indications for stretching exercises where a patient has treatable, functionally significant reductions in range of motion due to another disorder.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials,

randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Yoga has been used to treat fibromyalgia [659]

Yoga for Fibromyalgia

Yoga is recommended to treat fibromyalgia for highly motivated patients.

Sometimes Recommended.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications:	For highly motivated fibromyalgia patients. Should only be used in addition to an aerobic exercise program, rather than as a substitute.
Benefits:	Improved function and improved endurance.
Harms:	Negligible
Frequency/Dose/Duration:	Variable as yoga exercises have not been standardized. The regimen used in the highest quality study consisted of gentle poses, meditation, breathing exercises, yoga-based coping instructions, and group discussions 120min/weekly classes for 8 weeks [659].
Indications for Discontinuation:	Non-tolerance and/or non-compliance.
Rationale:	There is one moderate quality trial suggested efficacy compared with wait-listed controls [659], however wait-listed control studies are naturally biased in favor of the intervention. Yoga is not invasive, has negligible adverse effects, is low to moderate cost in aggregate depending on the degree of supervision, is thought to potentially benefit some patients, and is selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly;

systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Pilates has been used to treat fibromyalgia [660].

Pilates for Fibromyalgia

No Recommendation.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one low quality study suggesting potential efficacy [660]. Pilates is not invasive, has negligible adverse effects, is low to moderate cost in aggregate depending on the degree of supervision, has no quality evidence of efficacy and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are no quality studies on the usage of pilates for the treatment of fibromyalgia. There is a low-quality study listed in Appendix 4.

Aquatic therapy involves the performance of aerobic and/or flexibility and/or strengthening exercises in a pool to minimize the effects of gravity, particularly in situations where weight-bearing status is an issue [661]. Swimming has been used to treat fibromyalgia [662].

Swimming for Fibromyalgia

Sometimes Recommended.

Swimming is selectively recommended for select patients with fibromyalgia.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Indications:	Moderate to severe fibromyalgia, non-weight bearing status or partial weight-bearing (e.g., extreme obesity, significant hip/knee joint disease). May be selectively recommended for patients who prefer swimming over walking. Must be highly motivated.
Benefits:	Improved function, improved endurance, reduced fibromyalgia symptoms
Harms:	Negligible
Frequency/Dose/Duration:	50min/day, 3 days a week for 6 weeks. In infrequent cases, may need up to 12 weeks to become independent [662]. Target of 11 beats/min under anaerobic threshold. Should demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Subsequent progression to either 1) a land-based, self-directed physical activity or 2) self-directed swimming program by 6 weeks. If any membership to a pool is covered, coverage should be continued if it can be documented that the patient is using the facility at least 3 times a week and following the prescribed exercise program that is primarily aerobically-based.
Indications for Discontinuation:	Failure to attend, non-tolerance, failure to progress, or reaching a 4 to 6 week timeframe.
Rationale:	There is one trial suggesting comparable efficacy to a land-based walking program that targeted same heart rates and time commitments. There are circumstances where swimming may be indicated for treatment of patients with fibromyalgia. These include patients who are either non-weight-bearing, limited weight-bearing or unusual patients who are motivated and prefer swimming for aerobic exercise. Swimming is not invasive, has negligible adverse effects, is moderate cost in aggregate, has rationale for select indications, has evidence of efficacy, and thus is recommended for those who would comply with swimming.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials,

randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Aquatic therapy has been used for treatment of fibromyalgia [663, 664] [665] [661] [666] [667-670] including deep water running [671].

Aquatic Therapy for Fibromyalgia (Other than Swimming)

Recommended.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Indications:	Moderate to severe fibromyalgia, non-weight bearing status or partial weight-bearing.
Benefits:	Improved function, improved endurance, reduced fibromyalgia symptoms
Harms:	Negligible
Frequency/Dose/Duration:	One trial of deep water running, 60min sessions, 3x/wk targeted the anaerobic threshold for 40min of the session for 15 weeks [671]. Another study was of aquatic therapy 3 times/week at 50-80% of predicted heart rate maximum for up to 16 weeks [665]. Start with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Program should include up to 4 weeks of swimming or aquatic therapy with a significant aerobic component. Subsequent progression to a land-based, self-directed physical activity or self-directed aquatic therapy program by 6 weeks. For a minority of patients with fibromyalgia, aquatic exercise may be the preferred method. In these few cases, the program should become self-managed and if any membership to a pool is covered, coverage should be continued if it can be documented that the patient is using the facility at least 3 times a week and following the prescribed exercise program that is primarily aerobically-based.
Indications for Discontinuation:	Failure to attend, non-tolerance, failure to progress, or reaching a 4 to 6 week timeframe.

Rationale:	There are multiple trials suggesting efficacy of aquatic therapy of various components [664] [665] [666, 669, 670] including deep water running [671]. Components and structuring of the programs differed among the heterogeneous trials making direct comparisons difficult. Yet, the overall evidence is largely positive. There are circumstances where aquatic exercise may be indicated for treatment of patients with fibromyalgia. These include patients who are either non-weight-bearing, limited weight-bearing or highly motivated patients who prefer water-based exercises. Aquatic therapy is not invasive, has negligible adverse effects, is moderate cost in aggregate, has rationale for select indications, has evidence of efficacy and thus is recommended for those who would comply with aquatic therapy.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is moderate-quality evidence incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Tai Chi has been used for treatment of fibromyalgia [658, 672, 673].

Tai Chi for Fibromyalgia (not swimming)

Recommended.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Indications:	Fibromyalgia. The highest quality study exclusion included those with thyroid disease, and inflammatory arthropathies.
Benefits:	Improved FIQ scores, global assessment scores, 6-minute walk test results and depression symptoms.
Harms:	Negligible
Frequency/Dose/Duration:	The highest quality study used twice weekly sessions lasting 60 min. for 12 weeks [658]. 10-forms from classic Yang style of Tai Chi.

	Included warm-up, self-massage, breathing techniques, relaxation. Home Tai Chi prescribed for at least 20min/day.
Indications for Discontinuation:	Failure to attend, non-tolerance, failure to progress, or reaching a 4 to 6 week timeframe.
Rationale:	There are a few moderate quality trials. The highest quality suggested efficacy of Tai Chi compared with an education and stretching control group (Wang 10). Anotheuggested efficacy of Tai Chi compared with an educational control [672] for fibromyalgia, One trial of pool-based Tai Chi reported comparability to a stretching program [673]. Tai Chi is not invasive, has negligible adverse effects, is moderate cost in aggregate, has some evidence suggesting efficacy and thus is selectively recommended for those who would comply.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Spa therapy is heterogenous with numerous interventions that has been used for treatment of fibromyalgia [674, 675] [676]. Balneotherapy and mud baths have also been used for treatment of fibromyalgia [676, 677] [678-681] [682] [683] and may be combined with spa therapy.

Spa and Balneotherapy for Fibromyalgia

No Recommendation.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:	Spa therapy and balneotherapy are European-based treatments that are heterogenous in content, variously consisting of thalassotherapy, hot baths, exercise, education, etc. One trial flew patients from the Netherlands to Tunisia for sea-side spa treatments and claimed efficacy versus usual care [674]. One trial of balneotherapy used an in-pool exercise group, but did not target exercise, heart rate of anaerobic goals [684].

Spa and balneotherapy is/are not invasive, have negligible adverse effects, are high cost, have no quality evidence of efficacy, are largely not available in the US, and thus are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Mirror Therapy for Fibromyalgia

No Recommendation.

There is no recommendation for mirror therapy for treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**
Level of Confidence – **Low**

Rationale: There are not quality trials of mirror therapy for treatment of fibromyalgia and thus there is no recommendation for or against mirror therapy.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are no quality studies on the useage of mirror therapy for the treatment of fibromyalgia.

Whole Body Vibration for Fibromyalgia

Recommended.

There is no recommendation for or against whole body vibration to treat fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: One trial suggested additive benefits of whole body vibration plus exercise [685]. However, most of the remaining literature has minimal differences, is susceptible to usual care and contact time biases, and thus efficacy is unclear [686] [685, 687]. All trials were done in Spain, and availability and use in the US is limited. Whole body vibration device is not invasive, has minimal adverse effects, is moderate cost in aggregate, has limited evidence of efficacy that needs replication, and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Medications

NSAIDs have been used for treatment of fibromyalgia [688] [689] [690].

Oral NSAIDs for Fibromyalgia

Recommended.

Oral NSAIDs are selectively recommended for treatment of fibromyalgia.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Indications:	Fibromyalgia sufficiently severe to require medication. Generally should have been initially treated with aerobic exercises and anti-depressants. While NSAIDs may provide some synergistic effects with tricyclic antidepressants (Abrams 02), NSAIDs also may be less effective with SSRI antidepressants than other anti-depressants.
Benefits:	Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. NSAIDs are among the best pain medications especially for safety sensitive workers.
Harms:	Gastrointestinal adverse effects are especially prominent in those with past history of gastrointestinal bleeding, the elderly, and those with other diseases, e.g., diabetes mellitus and rheumatoid arthritis. For those, either cytoprotection or Cox-2 agents are advisable. There is some evidence for increased cardiovascular risks, especially in the highly and more-selective NSAID agents. There is no clear evidence of cardiovascular harm from the non-selective NSAIDs ibuprofen and naproxen. (see further discussion in Low Back Disorders Guideline). It appears that despite widespread usage, diclofenac does not have clear superiority at least for LBP where it has been trialed, yet may have increased risks for adverse cardiovascular events[188] and is neither recommended nor not recommended for use either alone or in combination with misoprostol (Arthrotec).
Frequency/Dose/Duration:	Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as second-line medications. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious for typical musculoskeletal disorders (see Low Back Disorders and Hip and Groin Disorders Guidelines). Over-the-counter (OTC) agents may suffice and may be tried first. COX-2 selective agents are recommended as a third- or fourth-line medications when there are contraindications for other NSAIDs and/or there are risks of GI complications; however, concomitant treatment with misoprostol, sucralfate, and proton pump inhibitors are also options for gastro-protection. For most patients, scheduled dosage, rather than as needed, may be preferable, however prescribing NSAIDs as needed is reasonable for mild or moderate symptoms. Due to the potential adverse effects from chronic use (more than 2 months) of NSAIDs, patients should be periodically monitored for adverse effects such as hypertension, blood loss, renal insufficiency (as manifested by an increased creatinine), and hepatic enzyme elevations. Older patients and those with co-morbidities generally require more frequent monitoring.
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.
Rationale:	There is no evidence of NSAID efficacy for the treatment of fibromyalgia. NSAIDs are not invasive, have low adverse effects in employed populations, are low cost, have evidence of efficacy for

multiple musculoskeletal disorders and thus are inferred to be mildly effective for fibromyalgia and are recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Comments:

Acetaminophen and paracetamol have been used for treatment of fibromyalgia [691, 692].

Acetaminophen for Treatment of Fibromyalgia

Sometimes Recommended.

Acetaminophen is recommended for select patients with fibromyalgia, particularly in patients with contraindications for NSAIDs.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications: Fibromyalgia sufficiently severe to require medication. Generally should have been initially treated with aerobic exercises and anti-depressants. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended for use unless the patient has a contraindication to NSAIDs. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious for typical musculoskeletal disorders and may be similarly less efficacious for fibromyalgia.

Benefits: Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. Acetaminophen is among the best medications especially for safety sensitive workers.

Harms: Negligible if used as prescribed in working age populations. Renal adverse effects are possible, especially among chronic, high-dose users and those with other renal impairment. Hepatic toxicity in high

	doses or among those with other hepatic impairments (e.g., excessive alcohol consumption). Reduced dosage may be used in such settings, along with close monitoring.
Frequency/Dose/Duration:	Generally prescribed up to 3.5g/day in divided doses, usually QID dosing
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.
Rationale:	There is one moderate quality trial suggesting mild reductions perceptions of noxious stimuli. There are no sizable quality trials of acetaminophen against placebo for treatment of fibromyalgia. Paracetamol, a close analog, has also not been studied for fibromyalgia, but does have evidence of efficacy for treatment of LBP, although not as successful as diflunisal,[189] mefenamic acid,[190] indomethacin,[190] or aspirin.[190] Thus, while the evidence suggests efficacy of acetaminophen and paracetamol, it appears these medications are modestly less efficacious than NSAIDs (although generally safer) at least for LBP. Acetaminophen is not invasive, has very low adverse effects, is low cost, has evidence of efficacy for treatment of LBP and is thought to have modest efficacy and thus is recommended for some patients with fibromyalgia.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Tricyclic antidepressants have been used for treatment of fibromyalgia [693-697] [698-700].

Norepinephrine Reuptake Inhibitor Anti-depressants (TCAs) for Fibromyalgia

Recommended.

Norepinephrine reuptake inhibitor anti-depressants (TCAs) are recommended for treatment of fibromyalgia.

Strength of Evidence – **Moderately Recommended, Evidence (B) –** Amitriptyline

Strength of Evidence – **Recommended, Evidence (C) –** Dothiepin, Esreboxetine

Strength of Evidence – **Recommended, Evidence (C) –** Amitriptyline combined with Fluoxetine

Level of Confidence – **High**

Indications:	Fibromyalgia sufficiently severe to require medication. Aerobic exercises are initially indicated and antidepressants may be indicated at the same initial visit depending on symptoms. Generally, antidepressants are trialed before NSAIDs. Some anti-depressants, e.g., some tricyclic and SNRIs may be used for their sedating properties for nocturnal sleep disturbance due the fibromyalgia.
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable if they include daytime somnolence; In those cases, the medication is generally inappropriate for safety sensitive jobs. However, many patients have improvements sleep and thus in daytime sedation. Cardiotoxicity.
Frequency/Dose/Duration:	Amitriptyline at a low dose at night and gradually increase (e.g., amitriptyline 25mg QHS, increase by 25mg each week) until sufficient effects are achieved, a sub-maximal or maximal dose is reached, or adverse effects occur. Trials have also been successful that did not escalate dose beyond starting dose of 25mg/day [697]. Esreboxetine 2mg/day, increase to 4mg/day at 2 weeks [701, 702]. Duration of use for pain associated with fibromyalgia patients may be indefinite, although some patients do not require indefinite treatment, particularly if they are compliant with progressive aerobic exercise.
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.
Rationale:	There is quality study suggesting efficacy of tricyclic anti-depressants for treatment of fibromyalgia, mostly for amitriptyline [703] [704] [697]. Data on long-term efficacy are lacking. Norepinephrine reuptake inhibiting anti-depressants (especially tricyclic antidepressants) are not invasive, have adverse effects that range from modest to intolerable, are low cost, have evidence of some efficacy for treatment of fibromyalgia and so are recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus,

CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Selective serotonin reuptake inhibitors have been used for treatment of fibromyalgia [705] [706-708].

Selective Serotonin Reuptake Inhibitors for Fibromyalgia

Moderately Recommended.

Selective serotonin reuptake inhibitors are moderately recommended for fibromyalgia patients.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **High**

Indications:	Fibromyalgia sufficiently severe to require medication, especially with depression. Aerobic exercises are initially indicated and antidepressants may be indicated at the same initial visit depending on symptoms. Generally, antidepressants are trialed before NSAIDs. If there is significant sleep disturbance, tricyclic antidepressants may be preferable.
Benefits:	Improved pain control, improved depression symptoms.
Harms:	Nausea, nervousness, anxiety, insomnia, increase risk of suicide. [709] Serotonin syndrome.
Frequency/Dose/Duration:	Fluoxetine 60mg QD-BID, although there appears to be either a minimal or no advantage of the BID dosing over the 60mg QD dosing. Other SSRI antidepressants include citalopram, escitalopram, fluvoxamine, paroxetine and sertraline [710-713][707][714]. Citalopram doses 20-40mg/day. Duration for patients with fibromyalgia may be as long as indefinitely, although some patients do not require indefinite treatment, particularly if they are compliant with progressive aerobic exercise.
Indications for Discontinuation:	Resolution, development of adverse effects, failure to adhere to a restoration program.
Rationale:	Multiple but not all moderate quality trials suggest SSRI antidepressants are effective for treatment of fibromyalgia in contrast with other pain disorders. Studies suggest reduction in symptoms of depression as well as modest reductions in pain. Data for citalopram conflict regarding efficacy [711, 712]. Data for paroxetine somewhat conflict regarding efficacy [714, 715]. SSRI antidepressants are not

	invasive, have low to moderate adverse effects, are moderate cost, have evidence of efficacy for fibromyalgia and thus are recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is a high-quality study and moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Duloxetine and milnacipran have been used for treatment of patients with fibromyalgia [701, 702, 716-737][722, 726, 738, 739][740-750]

Serotonin Norepinephrine Reuptake Inhibitors (e.g., Duloxetine, Milnacipran)

Moderately Recommended.

SNRIs are moderately recommended for limited use in fibromyalgia patients.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Indications:	Fibromyalgia sufficiently severe to require medication. Aerobic exercises are initially indicated and antidepressants may be indicated at the same initial visit depending on symptoms. Generally, antidepressants are trialed before NSAIDs, gabapentin or pregabalin. If there is significant sleep disturbance, SNRI or tricyclic antidepressants may be preferable. Adjunctive cognitive behavioral therapy is an option to provide adjunctive benefit [743].
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable and contributing to high dropout rates in the trials. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also have adverse effects including nausea, constipation, diarrhea, dizziness, fatigue, elevated heart rate, elevated blood pressure [738].

Frequency/Dose/Duration: Duloxetine 60mg QD [751, 752] and 120mg PO QD. [701, 752] Milnacipran 50mg BID to 100mg BID (100, 150, 200 mg/day) [733, 741]. Duration for patients with fibromyalgia may be as long as indefinitely [736], although some patients do not require indefinite treatment, particularly if they are compliant with progressive aerobic exercises.

Indications for Discontinuation: Resolution, adverse effects, improvement sufficient to not require medication.

Rationale: Many, but not all quality trials indicate SNRI antidepressants including duloxetine and milnacipran are effective for treatment of fibromyalgia [724, 752-755] [722, 723] [727] [729] [724, 730, 731, 733]; [735-737] [722, 726, 738, 739] [740-743, 745-750, 756]. SNRI antidepressants are not invasive, have moderate adverse effects, are moderate cost, have extensive evidence of efficacy for fibromyalgia and thus are recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Noradrenergic and Specific Serotonergic Antidepressants

Recommended.

The noradrenergic and specific serotonergic antidepressant, mirtazapine, is recommended for treatment of fibromyalgia.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

Indications: Fibromyalgia sufficiently severe to require medication. Aerobic exercises are initially indicated and antidepressants may be indicated at the same initial visit depending on symptoms. Generally, more traditional antidepressants are trialed before mirtazapine, yNSAIDs,

	gabapentin or pregabalin. If there is significant sleep disturbance, SNRI or tricyclic antidepressants may be preferable.
Benefits:	Improved pain control, may include reduced sleep disturbance. May reduce symptoms of depression.
Harms:	Sedating properties are prominent, as are constipation, dry mouth, weakness, dizziness, liver enzyme increase (ALT) and triglyceride increase.
Frequency/Dose/Duration:	Mirtazapine 15mg QHS for one week, then 30mg QHS. Duration for patients with fibromyalgia may be as long as indefinitely, although some patients do not require indefinite treatment, particularly if they are compliant with progressive aerobic exercises.
Indications for Discontinuation:	Resolution, adverse effects, improvement sufficient to not require medication.
Rationale:	There is one large, moderate quality trial suggesting substantial efficacy compared with placebo. Another smaller, placebo controlled trial also suggested efficacy [757]. Mirtazapine is not invasive, has moderate adverse effects, is moderate cost, has evidence of efficacy, and thus is selectively recommended for treatment of fibromyalgia.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Serotonin receptor antagonists have been used for treatment of fibromyalgia [699, 758-762]

Serotonin Receptor Antagonists for Fibromyalgia

No Recommendation.

There is no recommendation for serotonin reuptake antagonists for fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Studies substantially conflict. One short term trial of 5 days used IV administrations and suggested short term but no long term efficacy [758]; a second trial of 5 days suggested 2 weeks benefits [761]. Another trial suggested benefits of oral treatment for 10 days (Farber 01), but another trial suggested non-dose response relationships with response at 5mg but not at 10mg or 15mg [759]. Serotonin receptor antagonists are either oral or IV, have low to moderate adverse effects, are moderate to high cost in aggregate, have conflicting evidence of efficacy for fibromyalgia and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Bupropion, Trazodone, or Pramipexole for Fibromyalgia

No Recommendation.

There is no recommendation for the use of bupropion, trazadone, or pramipexole in fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is no quality evidence of efficacy of bupropion or trazodone for fibromyalgia. There is one trial of pramipexole suggesting efficacy, but no replication after over 10 years [763]. Bupropion and trazodone are not invasive, have low to moderate adverse effects, are low to moderate cost, but in the absence of efficacy, there is no recommendation for treatment of fibromyalgia.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly;

systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Atypical antipsychotics have been used for treatment of fibromyalgia [705, 764-766].

Atypical Antipsychotics for Fibromyalgia

No Recommendation.

There is no recommendation for the use of atypical anti-psychotics in fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:

Data are sparse and conflict regarding efficacy of atypical anti-pychotics for treatment of fibromyalgia [705, 764-766]. One trial suggests reduction in depression and pain [764]. One trial of adjunctive use suggested no reduction in pain but improved sleep and mood [766]. One comparative trial suggests inferiority to amitryptiline [765]. Atypical antipsychotics are not invasive, have moderate adverse effects, are low to moderate cost, but in the absence of efficacy, there is no recommendation for treatment of fibromyalgia. There may be limited indications involving failure of other medications such as progressive exercise, amitryptline, SNRI antidepressants, and gabapentin.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Memantine has been used for treatment of fibromyalgia [767, 768].

NMDA Receptor Antagonists for Fibromyalgia

No Recommendation.

There is no recommendation for the use of the NMDA receptor antagonist memantine in fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:	Data are sparse, with only 2 trials from one research group of memantine. One trial suggested modest reductions in pain [767] and a second study with small sample size suggested changes on MR spectroscopy [768]. Memantine is not invasive, has low adverse effects, is moderate cost, but with results from only one research group, a second trial from another group is needed for developing guidance on this topic, especially as there is evidence of efficacy for many other treatments.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Gabapentin and pregabalin have been used for treatment of fibromyalgia [701, 702, 720, 754, 769-774] [775-777] [778].

Anti-Convulsants for Fibromyalgia

Recommended.

Gabapentin and Pregabalin are recommended for treatment of severe fibromyalgia.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Indications:	Fibromyalgia sufficiently severe to require medication, often also having sleep disturbance. Aerobic exercises are initially indicated, and/or followed by antidepressants. Generally, antidepressants are trialed before NSAIDs. If there is significant sleep disturbance, SNRI or tricyclic antidepressants may be preferable. Having sufficient pain and other treatments have failed or results have been suboptimal so that generally considered a potential adjunct as a fourth- or fifth-line treatment, after attempting other treatments (aerobic exercise plus, e.g., antidepressant(s), NSAIDs, strengthening exercise, other exercise).
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also has adverse effects including nausea, vomiting, dizziness, nystagmus, ataxia.
Frequency/Dose/Duration:	Frequency and dosing are based on the medication prescribed. Gabapentin dosing in the highest quality study required titration at 300mg a day for 1 week at bedtime, then 300mg BID for 1 week, then 1,200mg/day for 2 weeks, then 600mg TID for 2 weeks, then 600mg BID, and 1,200mg QHS. If not tolerated, 2,400mg/day, dose reduced and mean dose 1,800mg/day [717]. Pregabalin dosing in the higher quality studies is 300-450 mg PO QD [779, 780], with an initial dose prescribed of 150mg PO QD. Duration of use for fibromyalgia patients may be indefinite, although many of these patients do not require indefinite treatment as the condition usually often resolves or improves.
Indications for Discontinuation:	Resolution of pain, lack of efficacy, or development of adverse effects. Monitoring of employed patients is indicated due to elevated risks for CNS-sedating adverse effects.
Rationale:	There are several quality trials suggesting efficacy of gabapentin and pregabalin for treatment of pain associated with fibromyalgia. [781, 782] One trial suggested efficacy of combined pregabalin plus paroxetine treatment, which was also superior to combinations with either amitriptyline or venlafaxine; another trial suggested combination of pregabalin with duloxetine was superior to monotherapy [783]. Gabapentin and pregabalin are not invasive, have significant adverse effects, are moderate cost, have some evidence of efficacy and so are selectively recommended for patients with fibromyalgia.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other

sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Glucocorticosteroids have been used for treatment of fibromyalgia [784].

Glucocorticosteroids for Fibromyalgia

Not Recommended.

Glucocorticoids are not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one low quality trial suggesting a lack of efficacy for prednisone [785]. Glucocorticoids are not invasive in oral forms, have high adverse effects, are low cost, but in the absence of evidence of efficacy, they are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is no quality evidence evaluating the usage of glucocorticosteroids for the treatment of fibromyalgia. There is low-quality evidence listed in Appendix 4.

DHEA has been used for treatment of fibromyalgia [786].

Dehydroepiandrosterone (DHEA) for Fibromyalgia

Not Recommended.

DHEA is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial suggesting a lack of efficacy for DHEA [786]. DHEA is not invasive in oral forms, has adverse effects, is low to moderate cost, has evidence of inefficacy and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Calcitonin has been used for treatment of fibromyalgia [787].

Calcitonin for Fibromyalgia

Not Recommended.

Calcitonin is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial suggesting a lack of efficacy for calcitonin [787]. Calcitonin is minimally invasive, has some adverse effects, is moderate cost, has evidence of inefficacy and thus is not recommended.

Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Vitamin D has been used for treatment of fibromyalgia [788].

Vitamin D for Fibromyalgia

Recommended.

Vitamin D is recommended for treatment of fibromyalgia.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

Indications:	Fibromyalgia patients with serum calcifediol <80nmol/L
Benefits:	Improved pain symptoms.
Harms:	Elevated calcium, weakness, fatigue
Frequency/Dose/Duration:	Dissolved in triglyceride solution, either: 2400 IU/day if serum calcifediol <60nmol/L, or 1200IU/day if calcifediol 60-80nmol/L. [788]. The quality trial re-evaluated calcifediol levels at weeks 5 and 13. The trial length was 20 weeks. A subsequent course may need to be instituted if symptoms worsen, particularly if vitamin D serum levels decrease. Ongoing treatment may be needed.
Indications for Discontinuation:	Sufficient improvement, completion of a course, adverse effects.
Rationale:	There is one moderate quality trial suggesting efficacy for treatment of fibromyalgia [788]. Vitamin D is not invasive, has low adverse effects, is low cost, has evidence of efficacy and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random

allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Melatonin has been used for treatment of fibromyalgia [789, 790].

Melatonin for Fibromyalgia

Recommended.

Melatonin is recommended for treatment of fibromyalgia.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

Indications:	Moderate to severe fibromyalgia with sleep disturbance. The sole quality trial required VAS pain scale score of at least 50mm.
Benefits:	Improved pain symptoms, improved sleep.
Harms:	Negligible
Frequency/Dose/Duration:	Melatonin 10mg QHS. May be combined with amitriptyline 25mg QHS as there is evidence of synergistic effects [790].
Indications for Discontinuation:	Sufficient improvement, completion of a course, adverse effects.
Rationale:	There is one moderate quality trial suggesting both efficacy for treatment of fibromyalgia and evidence of synergy with amitriptyline [790]. Melatonin is not invasive, has low adverse effects, is low cost, has evidence of efficacy and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100

abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Hormone replacement therapy has been used for treatment of fibromyalgia.

Hormone Replacement Therapy for Fibromyalgia

Not Recommended.

Hormone replacement therapy is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial suggesting lack of efficacy for treatment of fibromyalgia. Hormone replacement therapy is not invasive, has low adverse effects, is low cost, has evidence of inefficacy and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Raloxifen has been used for treatment of fibromyalgia [791].

Raloxifen for Fibromyalgia

Not Recommended.

Raloxifen is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There is no quality evidence. Raloxifen is not invasive, has adverse effects, is low to moderate cost, has no quality evidence and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of Raloxifen for the treatment of fibromyalgia. There is low-quality evidence listed in Appendix 4.

Oxytocin has been used for treatment of fibromyalgia [792].

Oxytocin for Fibromyalgia

Not Recommended.

Oxytocin is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial suggesting lack of efficacy for treatment of fibromyalgia [792]. Oxytocin is not invasive by nasal spray, has low adverse effects, is moderate cost, has evidence of inefficacy and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion,

406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Growth hormone has been used for treatment of fibromyalgia patients with low insulin-like growth factor [793-795].

Growth Hormone for Fibromyalgia

Recommended.

Growth hormone is selectively recommended for treatment of fibromyalgia.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

Indications:	Severe fibromyalgia, at least 5 years duration, with documented low insulin-like growth factor levels <160ng/mL. Negative evaluation for other pituitary diseases, including hormone evaluation and MRI. The highest quality trial also excluded major depression and diabetes mellitus [795]
Benefits:	Improved fibromyalgia symptoms, reduced numbers of tender points.
Harms:	Edema, arthralgia, muscle pain, diabetes, gynecomastia, carpal tunnel syndrome.
Frequency/Dose/Duration:	growth hormone 0.0125 mg/kg QD for one month. Dose adjusted monthly to maintain IGF-1 level of ~250ng/mL. One study was 9 months and another 12 months duration.
Indications for Discontinuation:	Sufficient improvement, adverse effects
Rationale:	Two moderate quality trials suggest efficacy in this select fibromyalgia patient population with low IGF-1 levels [793-795]. Growth hormone is minimally invasive, has significant adverse effects, is high cost, has evidence of efficacy in patients with low IGF-1 levels and thus is highly selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar,

and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Pyridostigmine has been used for treatment of fibromyalgia [796, 797].

Pyridostigmine for Fibromyalgia

Not Recommended.

Pyridostigmine is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: One moderate quality trial with two reports suggests lack of efficacy of pyridostigmine [796, 797]. Pyridostigmine is not invasive, has some adverse effects, is low cost, has evidence of inefficacy, and thus pyridostigmine is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Ritanserin has been used for treatment of fibromyalgia [798].

Ritanserin for Fibromyalgia

Not Recommended.

Ritanserin is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: One moderate quality trial suggests lack of efficacy of ritanserin [798]. Ritanserin is invasive, has some adverse effects, is low cost, has evidence of inefficacy, and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

S-adenosylmethionine has been used for treatment of fibromyalgia [799].

S-Adenosylmethionine for Fibromyalgia

Not Recommended.

S-adenosylmethionine is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: One moderate quality trial suggests lack of efficacy of S-adenosylmethionine (Jacobsen). S-methionine is not invasive, has some adverse effects, is low cost, has evidence of inefficacy, and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion

criteria. There is a high-quality study and moderate-quality studies incorporated into this analysis.

Creatine has been used for treatment of fibromyalgia [800].

Creatine for Fibromyalgia

No Recommendation.

There is no recommendation for creatine for treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial that suggested No differences in fibromyalgia pain and symptoms, although it was associated with improved muscle strength [800]. Creatine is not invasive, has low adverse effects, is low cost, has one trial suggesting no improvement in fibromyalgia scores although showing improved strength, and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Terguride has been used for treatment of fibromyalgia [801].

Terguride for Fibromyalgia

Not Recommended.

Terguride is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: One moderate quality trial suggests lack of efficacy of terguride [801]. Terguride is not invasive, has some adverse effects, is low cost, has evidence of inefficacy, and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Valcyclovir has been used for treatment of fibromyalgia [802].

Valcyclovir for Fibromyalgia

Not Recommended.

Valcyclovir is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: One moderate quality trial suggests lack of efficacy of valcyclovir [126]. Valcyclovir is not invasive, has some adverse effects, is low cost, has evidence of inefficacy, and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion

criteria. There is one moderate-quality study incorporated into this analysis.

Sodium oxybate, a salt of gamma hydroxybutyrate has been used for treatment of fibromyalgia [803-807].

Sodium Oxybate for Fibromyalgia

Recommended.

Sodium oxybate is moderately recommended for treatment of fibromyalgia.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Indications:	Severe fibromyalgia with sleep disturbance.
Benefits:	Reduced pain, reduced fatigue, improved sleep
Harms:	Nausea, extremity pain, dizziness, headaches, paresthesia, somnolence, renal and urinary disorders.
Frequency/Dose/Duration:	Sodium oxybate 4.5-6g QHS. [804] There was very little advantage of 6g compared with 4.5 g [805], but adverse effects were considerably higher.
Indications for Discontinuation:	Sufficient improvement, adverse effects, intolerance.
Rationale:	Several moderate quality trials suggest treatment of fibromyalgia with sodium oxybate improved pain, fatigue and sleep disturbance [803-807]. Sodium oxybate is not invasive, has significant adverse effects, is moderate cost, has evidence of efficacy for treatment of fibromyalgia, and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Zolpidem has been used for treatment of fibromyalgia [808].

Zolpidem has been used for treatment of fibromyalgia [808].

Zolpidem for Fibromyalgia

Not Recommended.

Zolpidem is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: One moderate quality trial suggests short-term treatment of fibromyalgia with zolpidem improved sleep, but had no effect on fibromyalgia symptoms [808]. Zolpidem is not invasive, has adverse effects, is low cost, has no evidence of inefficacy for treatment of fibromyalgia, and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Coenzyme Q has been used for treatment of fibromyalgia [809].

Coenzyme Q for Fibromyalgia

No Recommendation.

There is no recommendation for Coenzyme Q for treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one low quality trial suggesting some efficacy for coenzyme Q, but no quality trial suggesting efficacy [788]. Coenzyme Q is not invasive, has low adverse effects, is low cost, but in the absence of evidence of efficacy, there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of Coenzyme Q for the treatment of fibromyalgia.

Acetyl 1-carnitine has been used for treatment of fibromyalgia [810].

Acetyl 1-Carnitine for Fibromyalgia

No Recommendation.

There is no recommendation for acetyl 1-carnitine for treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial from 2007 that suggested differences after the midpoint of the trial favoring acetyl 1-carnitine [810]. However, at that same point, the dropout rates rose. The results have not been duplicated. Acetyl 1-carnitine is not invasive, has low adverse effects, is low cost, has one trial suggesting some potential promise, but has a study flaw that precludes an evidence-based conclusion, has not been replicated and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion

criteria. There is one moderate-quality study incorporated into this analysis.

Antidiencephalon has been used for the treatment of fibromyalgia [811].

Antidiencephalon for Fibromyalgia

No Recommendation.

There is no recommendation for antidiencephalon to treat fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is no quality evidence for antidiencephalon for treatment of fibromyalgia. Antidiencephalon is not invasive, has adverse effects, is low cost, has no quality evidence of efficacy to treat fibromyalgia and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of antidiencephalon for the treatment of fibromyalgia. There is low-quality evidence listed in Appendix 4.

Dolasetron has been used for the treatment of fibromyalgia [812].

Dolasetron for Fibromyalgia

No Recommendation.

There is no recommendation for dolasetron to treat fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications: Moderate or severe fibromyalgia.

Benefits:	Improvement in pain.
Harms:	Constipation. Other reported adverse effects included dizziness, nausea, fatigue, headache.
Frequency/Dose/Duration:	12.5mg IV, once a month for 4 months.
Indications for Discontinuation:	Sufficient improvement, completion of a course, intolerance, adverse effects
Rationale:	One trial of dolasetron suggested evidence of efficacy [812]. Dolasetron is invasive, has adverse effects, is moderate to high cost, and has only one trial suggesting efficacy. With IV administrations required, another trial of efficacy is needed for a recommendation.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Zopiclone, a non-benzodiazepine hypnotic, has been used for the treatment of fibromyalgia [813, 814].

Zopiclone for Fibromyalgia

No Recommendation.

There is no recommendation for zopiclone to treat fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:	There are two quality studies of zopiclone for treatment of fibromyalgia. The higher quality study suggested no improvement in fibromyalgia, although there was improvement in sleep [814]. The second study suggested some improvements in fibromyalgia [813]. All sleep medications may produce habituation, although zolpiclone does not produce physical dependency. Zopiclone is not invasive, has adverse effects, is low cost, has conflicting data regarding its utility to treat fibromyalgia and thus there is no recommendation. However,

there may be indications regarding sleep; yet, there are less habituating options to zopiclone for that indication.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Ondansetron has been used for the treatment of fibromyalgia [692].

Ondansetron for Fibromyalgia

No Recommendation.

There is no recommendation for ondansetron to treat fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one small trial of ondansetron in 1996 that has not been replicated [692]. Ondansetron is not invasive, has adverse effects, is low to moderate cost, has some preliminary evidence of efficacy but requires full size RCTs to confirm efficacy before a recommendation is able to be formulated.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion

criteria. There are no quality studies evaluating the usage of Ondansetron for the treatment of fibromyalgia. There is low-quality evidence listed in Appendix 4.

Skeletal muscle relaxants have been infrequently used for the treatment of fibromyalgia [815-820].

Skeletal Muscle Relaxants for Fibromyalgia

Not Recommended.

Skeletal muscle relaxants are not recommended for fibromyalgia patients.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies of skeletal muscle relaxants for treatment of fibromyalgia. There is one moderate quality trial suggesting potential for improved sleep with cyclobenzaprine 1-4mg QHS [816]. These agents may be counterproductive in patients with depression or dysthymia. One low quality trial reported a 50% dropout rate [817]. Skeletal muscle relaxants are not invasive, have adverse effects, are low cost, have no quality studies showing efficacy and so are not recommended for treatment of fibromyalgia.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Alpha1-antitrypsin has been reported as a potential risk regarding deficiency (Blanco 10), and also used for treatment of fibromyalgia.

Alpha1-Antitrypsin for Fibromyalgia

Not Recommended.

Alpha1-antitrypsin is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale:	One moderate quality trial found alpha1-antytripsin ineffective for treatment of fibromyalgia. Alpha1-antitrypsin is not invasive, has some adverse effects, is moderately costly, has evidence of lacking efficacy and thus is not recommended for treatment of fibromyalgia.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

There are numerous topical medications (capsaicin or sports creams) and patches used to treat chronic pain conditions.

Topical Medications and Lidocaine Patches

No Recommendation.

There is no recommendation for capsaicin and sports creams to treat fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:	Capsaicin and sports creams do not have quality evidence of efficacy. These agents are not invasive, have low adverse effects, are low cost, but in the absence of efficacy are not recommended for fibromyalgia.

Opioids

There is consensus that opioids are inappropriate medications for management of fibromyalgia. [821-826]

See Opioid Guideline.

Evidence: There are 3 moderate-quality RCTs incorporated into this analysis.

Devices

Many appliances have been used to treat chronic pain including kinesiotaping and taping, magnets and magnetic stimulation, and orthotics.

Kinesiotaping/Taping for Fibromyalgia

Not Recommended.

Kinesiotaping/taping is not recommended for fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Rationale: One moderate quality trial with 3-arms suggests no significant benefits of kinesiotaping compared with sham laser or active laser [827]. As laser therapy does not have quality evidence of efficacy, this also suggests kinesiotaping is ineffective. Taping is not invasive, has low adverse effects, is high cost, has no evidence of efficacy and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Magnets have been used for treatment of fibromyalgia [828].

Magnets/Magnetic Stimulation for Fibromyalgia

Not Recommended.

Magnets are not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Rationale:	There is one sham-controlled trial suggesting mostly negative results at 6 months [828]. Magnets and magnetic stimulation are not invasive, have low adverse effects, are moderately costly, have no evidence of efficacy and thus are not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Allied Health Therapies

Weight reduction has been used for treatment of fibromyalgia [829].

Weight Reduction

Recommended.

Weight reduction is recommended for treatment of fibromyalgia.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

Indications:	Obese patients with fibromyalgia

Benefits:	Improved FIQ score, depression, sleep quality and tender point count [829]
Harms:	Negligible
Frequency/Dose/Duration:	1200 kcal/day dietary instruction, with 12-20% protein, 50-55% carbohydrate, 30% fat calories in the quality study [829]
Indications for Discontinuation:	N/A
Rationale:	There is one moderate quality trial suggesting some efficacy for weight reduction [829]. Weight reduction instruction is not invasive, has negligible adverse effects, is low cost, has evidence of efficacy and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Gluten-free diet [830], vegetarian diet [831], have been used for treatment of fibromyalgia. Dietary glutamate [832] and micronutrient cocktails [833] have been used for treatment of fibromyalgia [832].

Dietary Interventions

No Recommendation.

There is no recommendation regarding gluten-free diets for treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:	There is one moderate quality trial suggesting comparable results between a gluten-free diet and a hypocaloric diet [830]. However, both groups experienced comparable weight reduction and evidence suggests weight reduction is effective [829], thus these study results are likely confounded. Gluten-free diet instruction is not invasive, has negligible adverse effects, is low cost, has no quality evidence of efficacy and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Music therapy has been used for fibromyalgia [834].

Music Therapy

No Recommendation.

There is no recommendation for the use of homeopathy in fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are two low quality studies of music therapy for treatment of fibromyalgia, both suggesting some potential efficacy [834]. Music therapy is self-administered, has no adverse effects, is low cost, has no quality evidence of efficacy and thus there is no recommendation. Threshold for attempting this form of treatment is low.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is no quality evidence evaluating the usage of music therapy for the treatment of fibromyalgia. There is low-quality evidence listed in Appendix 4.

Homeopathic treatments have been used for fibromyalgia [835-839].

Homeopathy

No Recommendation.

There is no recommendation for the use of homeopathy in fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies on homeopathy. Trials do not specify treatment(s), dose(s), etc. Homeopathy is not invasive, has generally low adverse effects, is moderate to high cost in aggregate, but has no quality evidence of efficacy and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is no quality evidence evaluating the usage of homeopathy for the treatment of fibromyalgia. There is low-quality evidence listed in Appendix 4.

There are many herbal and other treatments that have been used for fibromyalgia. Phytothermotherapy [840], horticulture therapy [841], electromagnetic shielding clothing [842], wool clothing [843], bright light therapy [844], Super malic (malic acid and magnesium) have been used for treatment of fibromyalgia.

Herbal, Alternative, Complementary or Other Preparations or Treatments

No Recommendation.

There is no recommendation for the use of Herbal or Other Preparations in fibromyalgia patients.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: There are no quality studies on herbal or other preparations in fibromyalgia patients although several herbal preparations have been

used to treat fibromyalgia. There is no recommendation for/against the use of harpagoside, willow bark (Salix), Camphora molmol, Melaleuca alternifolia, Angelica sinensis, Aloe vera, Thymus officinalis, Menthe piperita, Arnica Montana, Curcuma longa, Tanacetum parthenium, or Zingiber officinale for treatment of fibromyalgia.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is no quality evidence evaluating the usage of herbal or other preparations for the treatment of fibromyalgia. There is low-quality evidence listed in Appendix 4.

Reiki is considered by adherents to involve energy medicine and involves light touch and positive healing intention. It has been used for fibromyalgia [845].

Reiki

Not Recommended.

Reiki is not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial of Reiki suggesting no

adjunctive benefit for treatment of fibromyalgia [845].

Reiki is not invasive, has low adverse effects, is moderate cost in aggregate, has evidence of a lack of efficacy and thus is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly;

systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Qigong has been used for fibromyalgia [846][847-850].

Qigong

No Recommendation.

There is no recommendation regarding qigong for treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality trials of qigong for treatment of fibromyalgia. Qigong is not invasive, has low adverse effects, is moderate cost in aggregate, has no quality evidence of efficacy and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Acupuncture is based in part on the theory that many diseases are manifestations of an imbalance between yin and yang as reflected by disruption of normal vital energy flow (Qi) in specific locations, referred to as meridians. Needling along one of the 361 classical acupuncture points on these meridians is believed to restore the balance. Acupuncture has been utilized to treat fibromyalgia. (Yuan 16 [851-853]

Acupuncture

Sometimes Recommended.

Acupuncture is selectively recommended for use in patients with chronic moderate to severe fibromyalgia as an adjunct to more efficacious treatments.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Indications:	Acupuncture is selectively recommended for use in patients with chronic moderate to severe fibromyalgia as an adjunct to more efficacious treatments. Although not fully tested in a trial, one RCT's post-hoc analyses suggest beneficial effects are among those with lower pain thresholds. Patients should already have had a progressive aerobic exercise program instituted, been compliant with it, and should remain compliant with progressive aerobic exercises while undergoing acupuncture [854]. Also should have had prior anti-depressant medication(s) prescribed [854]. May have had other exercises and medication treatment(s).
Benefits:	Improved pain control with improved tolerance of exercises and resumption of normal daily activities.
Harms:	Negligible in experienced hands. However, pneumothorces and other severe complications have been reported from excessively deep penetrations.
Frequency/Dose/Duration:	An initial trial of 5-6 appointments in combination with a conditioning program of aerobic and possibly including strengthening exercises with measurement of objective outcomes. Data do not support traditional acupuncture over non-traditional acupuncture or simulated needle insertion [569, 756, 851, 852, 855, 856], raising questions about overall efficacy and suggesting different methods may be used. Further treatment should be based on ongoing objective improvement that is continuing throughout the treatment period. Additional treatments beyond the maximum should only occur based on progressively greater, incremental objective gains.
Indications for Discontinuation:	Resolution of symptoms, completion of a course of treatment, intolerance, non-compliance, including non-compliance with aerobic and strengthening exercises.
Rationale:	Two metanalyses reported no differences between real acupuncture and sham [851, 852], which is supported by the original studies [756, 855-857] There is evidence suggesting simulated needle insertion is equally efficacious [855], raising questions about overall efficacy of acupuncture for fibromyalgia. Electroacupuncture has been reportedly effective [856]. One study found acupuncture of additive benefit over traditional treatment [854]. One trial suggested acupuncture superior to fluoxetine at 4 weeks but not one year, although the inclusion criteria did not preclude prior SSRI treatment,

thus potentially biased against fluoxetine. Acupuncture is minimally invasive, has low adverse effects, has some quality evidence suggesting efficacy although there is no superiority of traditional acupuncture or simulated insertion raising concerns about overall efficacy of acupuncture for fibromyalgia. Thus acupuncture is selectively recommended as an adjunct to more efficacious treatments.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is a high-quality study and moderate-quality studies incorporated into this analysis.

Manipulation and mobilization are two types of manual therapy and have been used for treatment of fibromyalgia [654, 858-865].

Manipulation and Mobilization

No Recommendation.

There is no recommendation for the use of manipulation and mobilization to treat fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: One moderate quality trial found no differences after treatment of additive benefit of cervical manipulation to education, CBT and exercise [864], although after the trial, there were further improvements in the group that received manipulation that are not explained. There are no sizable quality studies indicating manipulation or mobilization are efficacious for treating patients with fibromyalgia. Manipulation and mobilization are not invasive, have generally lost adverse effects, are moderately costly in aggregate, have no quality evidence of efficacy and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random

allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Massage is commonly used for treatment of chronic muscular pain. Therapists commonly refer to massage as soft tissue mobilization. Massage may be used for various purposes including a mechanical effect on tissue, a circulatory effect, and an inhibitory effect. Massage is theorized to aid in muscle as well as mental relaxation, which could result in increased pain tolerance through endorphin release.[866] Massage has been used for treatment of fibromyalgia. [867-869]

Massage

Recommended.

Massage is recommended for use in select patients with moderate to severe fibromyalgia as an adjunct to more efficacious treatments.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications:	Massage is recommended for use in select patients with moderate to severe fibromyalgia as an adjunct to more efficacious treatments. Patients should already have had a progressive aerobic exercise program instituted, been compliant with it, and should remain compliant with progressive aerobic exercises while undergoing massage. Also should have had prior anti-depressant medication(s) prescribed. May have had other exercises and medication treatment(s).
Benefits:	Improved pain control with improved tolerance of exercises and resumption of normal daily activities.
Harms:	Negligible.
Frequency/Dose/Duration:	An initial trial of 5-6 appointments in combination with a conditioning program of aerobic and possibly including strengthening exercises with measurement of objective outcomes. Further treatment should be based on ongoing objective improvement that is continuing throughout the treatment period. Additional treatments beyond the maximum should only occur based on progressively greater, incremental objective gains.

Indications for Discontinuation:	Resolution of symptoms, completion of a course of treatment, intolerance, non-compliance, including non-compliance with aerobic and strengthening exercises.
Rationale:	There are no quality trials with sham massage or placebo treatment. There are multiple moderate quality trials suggesting superiority of massage to some comparative treatments such as amitriptyline. One randomized clinical trial showed Pilates was superior to massage [870]. Massage is not invasive, has low risk of adverse effects aside from short-term pain, [871] is moderately costly, and has some evidence of efficacy although inferiority to exercise. Thus, massage is recommended for select treatment of fibromyalgia only as an adjunct to an aerobic exercise program potentially additionally including strengthening exercises.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Myofascial release is a soft-tissue treatment technique that is most commonly used to treat myofascial pain. It has been used for treatment of fibromyalgia [872, 873].

Myofascial Release

Not Recommended.

Myofascial release is not recommended for fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications:	Chronic, moderate or severe fibromyalgia with inadequate treatment response to antidepressant(s), NSAIDs and exercise. Patients had pain limited activity at least one day/month.
Benefits:	Reduction in pain, FIQ scores, numbers of tender points

Harms:	May medicalize and remove focus from active exercises.
Frequency/Dose/Duration:	Twice weekly treatments of 10 myofascial release modalities for 20 weeks [872]
Indications for Discontinuation:	Completion of treatment course, non-compliance, intolerance
Rationale:	There is one moderate quality study suggesting reductions in tender points, FIQ scores and pain [872]. Myofascial release is not invasive, has low adverse effects, is moderate to high cost in aggregate, has some evidence of improvements in fibromyalgia patients and is thus selectively recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Reflexology is a complementary or alternative treatment that involves applying pressure to the feet and hands with specific thumb, finger, and hand techniques.

Reflexology

Not Recommended.

Reflexology is not recommended for fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale:	There is no quality evidence showing reflexology is efficacious in the treatment of fibromyalgia. Reflexology is not invasive, has negligible adverse effects, is moderately costly, but in the absence of evidence of efficacy is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random

allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is are no quality studies evaluating the usage of reflexology for the treatment of fibromyalgia.

Hot and cold therapies have been utilized primarily for treatment of acute musculoskeletal pain. However, they have also been used to treat patients with fibromyalgia. [874, 875]

Hot and Cold Therapies

No Recommendation

There is no recommendation for the use of hot and cold therapies to treat fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: There is no quality evidence evaluating heat and cryotherapies for treatment of fibromyalgia. There is one moderate quality trial of halogen lamp heating unit in addition to multimodal treatment was superior to the treatment alone, but there was no sham or similar control treatment [875]. Non-proprietary, self-applications are not invasive, have low adverse effects provided excessive cold or heat are not used, and may have no associated costs. However, there are other treatment strategies with demonstrated efficacy in the treatment of fibromyalgia and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Hyperbaric oxygen has been used for treatment of fibromyalgia [876].

Hyperbaric Oxygen

No Recommendation.

There is no recommendation for hyperbaric oxygen for treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial suggesting some efficacy for HBO, but it had no sham HBO arm, raising questions of efficacy [876]. HBO is not invasive, has mostly low adverse effects, is high cost, but in the absence of clear evidence of efficacy, there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Combined interferential and ultrasound has been used to treat fibromyalgia [877] [878].

Electrical Therapies

Interferential and Ultrasound

No Recommendation.

There is no recommendation for interferential and ultrasound therapies for fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality sham-controlled trials. There is one moderate quality trial of once vs. twice weekly combined treatments with no differences between the groups, raising questions of inefficacy. These therapies are not invasive, have low adverse effects, are moderately

costly depending on numbers of treatments, have no quality evidence of efficacy and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Pulsed electromagnetic therapy has been used for treatment of fibromyalgia [879-882]

Pulsed Electromagnetic Therapy

No Recommendation.

There is no recommendation for pulsed electromagnetic therapy for fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one moderate quality study suggesting potential short term efficacy [879]. There do not appear to be intermediate to long term benefits. Pulsed electromagnetic therapy is not invasive, has low adverse effects, is moderate to high cost in aggregate. While there is some limited evidence suggesting efficacy, prior to a recommendation, another quality sizable trial from another research group is needed.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from

Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Cranial electrical stimulation has been used for treatment of fibromyalgia [883, 884].

Microcurrent Cranial Electrical Stimulation

No Recommendation

There is no recommendation for microcurrent cranial electrical stimulation for fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial with 3 graphs possibly suggesting efficacy, but no table of results presented [885]. Cranial electrical stimulation is not invasive, has low adverse effects, is moderate cost in aggregate and there are no reports with data provided, thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Cortical electrostimulation has been used for treatment of fibromyalgia [886, 887]

Cortical Electrostimulation

No Recommendation

There is no recommendation for cortical electrostimulation for fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one low quality trial with 2 reports [886, 887] that appears to have a randomization failure. Cortical electrostimulation is not invasive, has low adverse effects, is moderate cost in aggregate and in the absence of quality data, there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is no quality evidence evaluating the usage of cortical electrostimulation for the treatment of fibromyalgia.

Transcranial direct current stimulation has been used for treatment of fibromyalgia [888][889][890][891].

Transcranial Direct Current Stimulation

No Recommendation.

There is no recommendation for transcranial direct current stimulation for fibromyalgia.

Strength of Evidence – **No Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Nearly all moderate quality trials were 5 days or less and thus essentially hypothesis generating [889, 890, 892][891]. One moderate quality trial suggested short term benefit of combined stimulation with aerobic exercise, but aerobic exercise alone trended to be superior at 1 month. Transcranial direct stimulation is not invasive, has low adverse effects, is moderate cost in aggregate and only one moderate quality trial suggests a short term benefit which is gone at 1 month, thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies.

We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Transcranial magnetic stimulation has been used for treatment of fibromyalgia [893][894-897][898].

Transcranial Magnetic Stimulation

Not Recommendation

Transcranial magnetic stimulation is not recommended for fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: The highest quality trial suggests a lack of efficacy [898]. Many but not all other moderate quality studies suggest lack of efficacy to reduce pain [893][894, 895, 897, 899]. Transcranial magnetic stimulation is not invasive, has low adverse effects, is moderate to high cost in aggregate and most trials suggest lack of efficacy including the highest quality trial, thus transcranial magnetic stimulation is not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Low-level laser treatment has been used to treat fibromyalgia [900] [827, 901][902, 903].

Low-Level Laser Therapy

Not Recommended

Low-level laser therapy is not recommended for fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Rationale:	There are a few moderate quality studies evaluating the use of low-level laser therapy to treat fibromyalgia. Two moderate quality trials suggest a lack of benefit compared with sham [827, 903], with one of them also finding comparable results with kinesiotaping [827]. One moderate quality trial suggested no additive benefit of laser over stretching exercises alone [904]. Low- level laser Low level laser therapy is not invasive, has negligible adverse effects, is high cost, has moderate quality evidence of a lack of efficacy, and thus is not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Multiple forms of electrical therapies have been used to treat fibromyalgia including transcutaneous electrical stimulation (TENS), percutaneous electrical nerve stimulation (PENS), microcurrent electrical stimulation, H-Wave® Device Stimulation, and interferential therapy. The mechanism(s) of action, if any, are unclear. TENS has been used to treat fibromyalgia [905-907].

Transcutaneous Electrical Nerve Stimulation (TENS)

No Recommendation.

There is no recommendation for the use of TENS to treat fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:	There are three moderate quality trials, only one of which is sham-controlled. The sham-controlled trial is hypothesis generating as it consisted of only one treatment and even though aspects of it suggested potential efficacy, it is thus not usable for guidelines development [905]. One moderate quality trial with sparse methods suggested pain reductions over one week, and no longer followup [907]. The other trial had no sham arm and found comparable efficacy with superficial warmth [906], raising questions about efficacy. TENS is not invasive, has low adverse effects, is moderate cost, and in the absence of evidence of efficacy there is no recommendation. Sham controlled trials with at least moderate follow-up intervals are needed to provide a recommendation.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Other forms of electrical therapies have been used to treat fibromyalgia including, percutaneous electrical nerve stimulation (PENS), microcurrent electrical stimulation, H-Wave® Device Stimulation, and interferential therapy.

Other Electrical Therapies

Not Recommended.

Other forms of electrical therapies are not recommended for fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale:	There are no quality studies evaluating the use of electrical therapy to treat fibromyalgia. These therapies are not invasive, have low adverse effects, are moderate to high cost, have no quality evidence of efficacy, do not address the central mechanism of pain, and are not recommended for treatment of fibromyalgia.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of electrical therapy for the treatment of fibromyalgia.

Iontophoresis uses electrical current to transdermally deliver medications, most typically such as glucocorticosteroids and NSAIDs.

Iontophoresis

Not Recommended.

Iontophoresis is not recommended for fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale:	There are no quality studies evaluating the use of iontophoresis to treat fibromyalgia. Iontophoresis is not invasive, has low adverse effects, is moderately costly, has no quality evidence of efficacy, does not address the central mechanism of pain, and is not recommended for treatment of fibromyalgia.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669

in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of iontophoresis for the treatment of fibromyalgia.

Ganglion blocks have been used for treatment of fibromyalgia [908, 909].

Injection Therapies

Ganglion Blocks

Not Recommended.

Ganglion blocks are moderately not recommended for fibromyalgia.

Strength of Evidence – **Moderately Not Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Rationale: There are two quality studies suggesting lack of efficacy of spheno-palatine ganglion blocks [908, 909]. Ganglion blocks are invasive, have adverse effects, are moderate to high cost depending on number of injections administered, have evidence of inefficacy, and thus are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.

Ketamine infusions have been used for treatment of fibromyalgia [910].

Ketamine Infusions

Not Recommended.

Ketamine infusions are not recommended for treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale:	There is one moderate quality trial comparing ketamine with midazolam and finding some differences over a few hours, but no significant differences from 2-8 weeks [911]. Ketamine infusions are invasive, have adverse effects, are moderate to high cost depending on number of infusions, have evidence of inefficacy, and thus are not recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Lidocaine infusions have been used for treatment of fibromyalgia [700, 912].

Lidocaine Infusions

Not Recommended.

Lidocaine infusions are not recommended for the treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Moderate**

Rationale:	There are two quality studies suggesting lidocaine infusions are ineffective for treatment of fibromyalgia [912]. These injections are invasive, have adverse effects, are moderate to high cost depending

on number of injections administered, have evidence of inefficacy, and thus are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusio4, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Implantable nerve stimulation has been used for treatment of fibromyalgia [913].

C2 Nerve Stimulation

No Recommendation.

There is no recommendation for C2 nerve stimulation for the treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one 2-week crossover trial of an implantable stimulator device with sparsely reported results and methods [913]. The implantable stimulator device is invasive, 50% reportedly had adverse effect(s), is high cost, has no intermediate or long term quality evidence of efficacy and thus there is no recommendation.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles

considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Prolotherapy injections attempt to address a theoretical cause or mechanism for chronic pain. They involve repeated injections of irritating, osmotic, and chemotactic agents (e.g., dextrose, glucose, glycerin, zinc sulphate, phenol, guaiacol, tannic acid, pumice flour, sodium morrhuate), combined with an injectable anesthetic agent to reduce pain, into back structures, especially ligaments, with the theoretical construct that they will strengthen these tissues. Prolotherapy has been used for treatment of fibromyalgia [914, 915]

Prolotherapy Injections

Not Recommended.

Prolotherapy Injections are not recommended for the treatment of fibromyalgia,

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Rationale: There are no quality studies documenting benefits of prolotherapy for treatment of fibromyalgia. These injections are invasive, have some adverse effects, are moderate to high cost depending on number of injections administered, have no quality evidence of efficacy, do not treat the theoretical central mechanism of pain, and thus are not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is no quality evidence evaluating the usage of prolotherapy injections for the treatment of fibromyalgia.

Behavioral and Psychological Interventions

Self-management has been used for treatment of fibromyalgia [916][917-919].

Self-Management

No Recommendation.

There is no recommendation for self-management for the treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:	There are two moderate quality trials that both have a wait-list control bias, thus a bias in favor of finding efficacy of self-management. Yet, despite those biases, the two studies conflict regarding whether self management is effective for fibromyalgia [918] [919]. Self-management is not invasive, has negligible adverse effects, has conflicting evidence on efficacy and thus there is no recommendation.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Body awareness and self-awareness has been used for treatment of fibromyalgia, especially as a co-intervention in trials of other treatments such as pilates, yoga, and multi-modal treatments [920-922].

Body Awareness and Self-Awareness

No Recommendation

There is no recommendation for body awareness and self-awareness for the treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Two small studies substantially conflict regarding efficacy [921, 922]. Other trials including body awareness show variable results, although inclusion of active exercise is associated with mostly positive results. Body awareness and self awareness is not invasive, has negligible adverse effects, has conflicting evidence of efficacy and thus there is no recommendation as a stand alone intervention.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Attention modification has been used for treatment of fibromyalgia [923] [924].

Attention Modification

Not Recommended

Attention modification is not recommended for the treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial suggesting a lack of efficacy of attention modification [923]. Attention modification is not invasive, has negligible adverse effects, has evidence of a lack of efficacy and is thus not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554

from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Guided imagery has been used for treatment of fibromyalgia [925-929].

Guided Imagery

Not Recommended.

Guided imagery is not recommended for the treatment of fibromyalgia.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial suggesting a lack of efficacy of guided imagery [925]. Guided imagery is not invasive, has negligible adverse effects, has evidence of a lack of efficacy and is thus not recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Virtual Reality

No Recommendation

There is no recommendation for virtual reality for the treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies of virtual reality for treatment of fibromyalgia. One moderate quality study suggested inferiority to

	shared-decision making. In the absence of quality evidence compared with sham or other intervention of known level of efficacy, there is no recommendation.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Mindfulness therapy involves increasing awareness and acceptance of aversive and other experiences, thus improving coping and overcoming symptoms and debilities associated with fibromyalgia. It has been proposed as an alternate to cognitive behavioral therapy. Mindfulness intervention has been used for treatment of fibromyalgia [930, 931][932-934].

Mindfulness Intervention

Recommended.

Mindfulness intervention is recommended for the treatment of fibromyalgia.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications:	Fibromyalgia, especially moderate or severe.
Benefits:	Reduced symptoms, depressive symptoms, stress, treatment costs, and disability pensions
Harms:	Negligible
Frequency/Dose/Duration:	Trials have used computer-based methods [930], as well as sessions. Sessions have included 2.5-hours for 8 weeks [931]
Indications for Discontinuation:	Completion of a training course, sufficient improvement, non-compliance
Rationale:	There are multiple low quality trials involving mindfulness therapy, with this preliminary evidence suggesting reductions in fibromyalgia symptoms [932], depressive symptoms [931], stress [932] and reduced

	disability pensions. Mindfulness therapy is not invasive, has negligible adverse effect(s), is low to moderate cost in aggregate and depending on numbers of appointments, has no quality data of efficacy, has low quality evidence suggesting considerable benefits, and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of mindfulness interventions for the treatment of fibromyalgia. Low-quality evidence is listed in Appendix 4.

Acceptance and commitment therapy has been used for treatment of fibromyalgia. This treatment includes acceptance and/or willingness to experience as a behavioral response to pain; preparing for behavior change; clarification of life values; short- and long-term behavioral goals, and; acceptance and cognitive defusion emphasizing utility of more flexible behavioral relationship with pain and distress.

Acceptance and Commitment Training

Recommended.

Acceptance and commitment training is recommended for fibromyalgia, especially moderate or severe.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications:	Fibromyalgia, especially moderate or severe.
Benefits:	Reduced fibromyalgia symptoms, depressive symptoms, anxiety symptoms.
Harms:	Negligible
Frequency/Dose/Duration:	12 weekly group sessions has been used in one quality study.
Indications for Discontinuation:	Completion of a training course, sufficient improvement, non-compliance

Rationale:	There are a couple trials suggesting efficacy [935], although with likely exercise and activity cointerventions. One trial found comparable effects with cognitive behavioral therapy [935]. Acceptance and commitment training is not invasive, has negligible adverse effect(s), is moderate cost in aggregate, has some quality data suggesting efficacy, and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Psychoeducational treatment programs have been used for treatment of fibromyalgia [936, 937].

Psychoeducational Treatment

Recommended.

Psychoeducational treatment programs are recommended for fibromyalgia, especially moderate or severe.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications:	Fibromyalgia, especially moderate or severe.
Benefits:	Improved physical function, mental health; reduced symptoms, depressive symptoms, stress, treatment costs, and disability pensions
Harms:	Negligible
Frequency/Dose/Duration:	One trial consisted of 2 one-on-one sessions [938]. Trials have used computer-based methods [930], as well as sessions. Sessions have included 2.5-hours for 8 weeks [931]
Indications for Discontinuation:	Completion of a training course, sufficient improvement, non-compliance

Rationale: Trials suggest a psycho-educational and pain educational programs for fibromyalgia are associated with improved global functional status and lower costs [936-938]. Components of the programs differ. Pyschoeducational programs are not invasive, have negligible adverse effect(s), are moderate cost in aggregate, have some quality data of efficacy, and thus are recommended.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Written education materials and disclosure assignments have been used for treatment of fibromyalgia [939-942]

Written Pain Education and Disclosures

No Recommendation.

There is no recommendation for the use of written education materials and disclosure assignments in the treatment of fibromyalgia.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one moderate quality trial suggesting a lack of efficacy of one particular formal written education booklet [939]. Providing written educational materials is not invasive, has negligible adverse effects, has one trial suggesting one booklet lacked efficacy, other succinct materials may be effective, and thus there is no recommendation. Providing some written materials is advisable for patients for essentially all disorders. The sole quality fibromyalgia trial's use of a 15pp booklet may have been too long for that which patients will read currently and/or content may have had issues.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random

allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Shared decision-making has been evaluated for treatment of fibromyalgia [943, 944].

Shared Decision Making

Recommended.

Shared decision making is recommended for the treatment of fibromyalgia.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – **Low**

Indications:	All fibromyalgia patients
Benefits:	Improved engagement, coping and satisfaction.
Harms:	Negligible
Frequency/Dose/Duration:	inclusion in all clinical visits
Indications for Discontinuation:	Patients who prefer to not be involved in shared decision-making.
Rationale:	One moderate quality trial suggests improved coping, although health outcomes were comparable regardless of shared decision-making [943]. Shared decision-making is not invasive, has negligible adverse effect(s), is low cost, has some quality data suggesting potential efficacy, and thus is recommended.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: fibromyalgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,046 articles in PubMed. We retrieved 5,669 in Scopus, 426 in CINAHL, 18,300 in Google Scholar, and 0 from other sources. Due to the large volume of abstracts/titles in Scopus, CINAHL, and Google Scholar, we conducted a thorough review of the first 100 abstracts/titles in those databases. We considered for inclusion 554 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 0 from other sources. Of the 554 articles considered for inclusion, 406 randomized trials and 148 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Treatment Evidence Tables

Exercise

Evidence for Aerobic Exercise

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
McCain, 1988 (Score=6.5)	Aerobic	RCT	Sponsored by the Canadian Arthritis Society. No mention of COI.	N = 42 with primary Fibromyalgia	Mean age: 38.36 years; No gender data.	Cardiovascular fitness (CVR) (n=18) – Patients met in a group setting and received CVR training for 60 minutes 3 times each week for 20 weeks. vs. Flexibility exercises (FLEX) (n=20) – Patients met in a group setting that targeted flexibility measures for 60 minutes 3 times each week for 20 weeks.	19 months.	Fitness training resulted in improved peak work capacity scores (+168.7± 166.8 vs. -7.3±7.9 kilopond-meters, p <0.001), as well as reduced pain threshold scores for palpation (p = 0.04). Nine patients (50%) in cardiovascular fitness group felt they moderately or markedly improved vs. two (11.1%) in flexibility exercises. Physician assessments of moderate or marked improvement 35% vs. 5.6%.	"Patients with primary fibromyalgia who achieve enhanced cardiovascular fitness after strenuous physical activity have modest improvements in both subjective and objective measurements of pain."	Blinding of exercises attempted between two patient groups, but effective blinding seems somewhat dubious. Baseline differences included younger age and higher pain intensity scores among cardiovascular fitness group.

Baptista 2012 (6.0)	Aerobic Exercise	RCT	Received Scholarship from CAPES. No mention of COI.	80 patients diagnosed with fibromyalgia using American College of Rheumatology criteria.	0 males, 80 females; Mean age for intervention group 49.5.	Intervention Group (N=40) Dance group that participated in one-hour weekly belly dance classes. Vs Control Group (N =40) patients did not receive treatment but just were evaluated at the predetermined times.	Follow up at baseline, 16 weeks, and 32 weeks.	Visual Analogue Scale (VAS), control vs intervention group, Week 16: 7.5±1.4 vs 4.6±2.0. Week 32: 7.3±1.7 vs 4.7±2.6 (p<0.001). 6 min walk test, control vs intervention (m), Week 16: 344.3±72.7 vs 443.5±78.3. Week 32: 343±77.9 vs 431±88.7 (p<0.001). Fibromyalgia Impact Questionnaire (FIQ), control vs intervention group, Week 16: 6.61±1.53 vs 4.69±1.73. Week 32: 5.9±1.86 vs 4.26±1.81 (p<0.001). Short form 36-item questionnaire (SF-36) Pain section, control vs intervention, Week 16: 25.1±14.2 vs 44.7±20.7. Week 32: 29.1±21.1 vs 46±19.2 (p<0.001). SF-36	"[W]e therefore conclude that belly dance leads to improvements in pain, sleep pattern, functional capacity, and self-image in patients with fibromyalgia. The improvement in quality of life and patient adherence the activity make, belly dance a safe, effective therapeutic strategy for women with fibromyalgia."	Waitlist control bias, baseline comparability has significant differences between groups. Data suggest belly dance may be used to decrease pain and improve symptoms associated with fibromyalgia.

								emotional aspects section, control vs intervention, week 16: 17.5±26.1 vs 55±33.6. Week 32: 31.5±38.7 vs 51.9±39.6 (p=0.003). SF-36 Mental Health section, control vs intervention, Week 16: 44.5±26.6 vs 54.2±20.7. Week 32: 46.2±22.6 vs 52.3±20.8 (p=0.021).		
Schacter, 2003 (Score=5.5)	Aerobic	RCT	Sponsored by the Saskatchewan Health Services Utilization and Research Commission, Canada. No mention of COI.	N = 143 sedentary females with Fibromyalgia	Mean Age: 41.83 years; 0 males, 143 females.	NE (n=36) vs. SBE (n=56) – Participants performed 2 15-minute bouts of aerobic exercise a day separated by 4 hours for 16 weeks. Vs. LBE (n=51) – Participants performed a 30-minute	No follow up.	FIQ total scores (baseline/post-test): no exercise group (5.5±1.3/ 5.4±1.6) vs. short bouts (5.4±1.5/5.2±1.8) vs. long bout (5.6±1.4/ 5.1±1.7). Blinded physician ratings of global severity were: no exercise (5.3±1.6/ 4.8±1.6) vs. short bouts (4.9±1.7/4.2±1.7) vs. long bout (5.1±1.7/ 4.4±1.8). VAS pain ratings: no	"Progressive, home-based, low-impact aerobics improved physical function and fibromyalgia symptoms minimally in participants who completed at least two thirds of the recommended exercise. Fractionation of exercise training provided no advantage in terms of exercise adherence, improvements in fibromyalgia	

						bout once daily for 16 weeks. Programs designed to include videotapes. Researchers contacted subjects to encourage participation and work through barriers to compliance.		exercise (6.1±2.0/5.6±2.2) vs. short bouts (5.7±2.3/ 5.8±2.5) vs. long bout (5.8±1.8/5.3±2.3).	symptoms or physical function. High attrition rates and problems with exercise adherence were experienced in both exercise groups."	
King, 2002 (Score=5.5)	Aerobic	RCT	Sponsored by the Medical Services Incorporated Foundation and from the Health Services Research and Innovation Fund, Alberta Health. No mention of COI.	N = 152 females with Fibromyalgia (ACR criteria used)	Mean age: 49.74 years; 0 males, 152 females.	Exercise (n=46) – Participants met 3 times per week for a supervised aerobic exercise program consisting of walking, aquasize, or low impact aerobics for 12 weeks. vs. Education (n=48) – Participants met once a week for 2 hours for a program on self-	3 months.	At 20 weeks, all patients in the exercise group felt the exercise had "increased their feelings of general well-being." Strength measures increased more in the exercise group, but not statistically significantly. Exercise induced pain decreased in most measures in the exercise group compared with the control group, with some measures decreasing statistically significantly.	"Subjects receiving the combination of exercise and education and who complied with the treatment protocol improved their perceived ability to cope with other symptoms. In addition, a supervised exercise program increased walking distance at post-test, an increase that was maintained at follow up in the exercise-only group."	

						management for 12 weeks. vs. Exercise and Education (n=37) – patients received both exercise and education interventions for 12 weeks. vs. Control (n=39) – Participants received instructions on basic stretches and 5 items on general coping strategies for 12 weeks.				
Sañudo 2010 (5.5)	Aerobic Exercise	RCT	Sponsored by the University of Seville. No COI.	64 patients diagnosed with fibromyalgia using American College of Rheumatology criteria.	0 males, 64 females; Mean age in AE group 55.9±1.6, CE group 55.9±1.7, and control group 56.6±1.9.	Aerobic Exercise Group (AE) (N=22) which did 2 weekly sessions of 45-60 minutes. Vs Combined Exercise group (CE) (N=21) Did AE sessions for 15-20 minutes and combined with	Follow up at baseline and 24 weeks.	Fibromyalgia Impact Questionnaire (FIQ) score improvement, baseline vs 24 wks, AE & CE: 8.8±14 & 8.8±12 (p<0.20). Beck Depression inventory (BDI) improvement baseline to 24 wks, AE and CE: 8.5±8 (p<0.001) & 6.4±4 (p<0.001). SF-36	"Given the equivalent time commitment required for the AE and CE interventions, our results suggest that women with a diagnosis of FMS can gain additional health benefits by engaging in combined supervised strength,	Usual Care Bias. Unclear if FM participants had different length of time since diagnosis of fibromyalgia. Data suggest both exercise groups improved.

						muscles strengthening exercises vs Control group (control) (N=21) typical medical treatment and no deviation from normal daily routines.		score improvement, baseline to 24 wks, AE and CE: 8.9±10 & 8.4±11 ($p<0.01$). CE hand strength better than controls ($p<0.012$). Generally greater effect size differences were observed in the CE group.	flexibility, and aerobic exercise."	
Hooten 2012 (5.5)	Aerobic Exercise	RCT	Sponsored by a CR-20 grant from the Mayo foundation. No COI.	N=72 patients diagnosed with fibromyalgia using American College of Rheumatology criteria.	7 males, 65 females; Mean age of aerobic group is 45.8±11.5 and strength group is 47.3±10.1.	Strength Training Group (N=36) upper and lower main muscle group strength exercises were performed daily for 25-30 minutes under supervision of Physical therapist. vs Aerobic Training group (N=36) patients used a stationary bicycle to eventually get to 70% max HR.	Baseline and week 3.	Mean Pain severity change at week 3, intention to treat analysis, Aerobic group and strength group: 11.0 (95% CI 6.4 - 15.6) and 12.0 (95% CI 7.0 - 17.0). No significant difference in between groups for pain severity in fibromyalgia.	"This study found that strength and aerobic exercise had equivalent effects on reducing the pain severity among patients with fibromyalgia."	Data suggest comparable efficacy between aerobic vs strengthening exercises on pain severity.

Stephens 2008 (5.5)	Aerobic Exercise	RCT	Sponsored by the Hospital for Sick Children Foundation and by a complementary	N=30 children 8-18 and were diagnosed with fibromyalgia.	8 males, 22 females; Mean age in qigong group is 12.9±2.7 and aerobics group 13.6±1.8.	Qigong Group (N=16) participants did 3 weekly sessions (1 supervised, 2 unsupervised) qigong (Low impact posture exercises) workouts for 12 weeks. vs Aerobics group (N=14) participated in 30 minutes of boxing/cardio-dance movements with a goal of achieving 70% max HR.	Follow up at baseline and 12 weeks.	Childhood Health assessment questionnaire (C-HAQ) aerobic group was superior to qigong group in physical function scores and in severity of illness and pain: (F [1,22] = 4.4, p=0.05) and (F [1,21] = 5.32, p=0.03) and (F [1,21] = 9.75 p=0.005), respectively. PedQL fatigue section aerobics group improved more (F [1,22] = 7.96, p=0.01). Overall Quality of Life (QoL) aerobics group had superior improvement (F [1,22] = 6.50, p=0.01).	"The results of this randomized controlled pilot trial of a 12 week exercise intervention suggest that it is feasible and safe for children with FM to participate in a moderate-intensity aerobic exercise program. Exploratory analyses suggest that aerobic exercise may be beneficial in reducing plain, improving QOL, decreasing FM symptoms of fatigue, and increasing physical function in children with FM.	Small sample pilot study. Sample aged 8-18 mean age =14. Data suggest improved physical function, less fatigue and better quality of life in aerobics group.
Kayo A, 2012 (5.5)	Exercise	RCT	No sponsorship or COI.	N = 90 patients with fibromyalgia.	The mean age of the WA group was 47.7 years. The mean age of the MS group was 46.7 years. The mean age of the	Walking Program (WA) (n=30) – patients walked every day for 25 to 40 mins. The intensity increased every 4 weeks. Vs. Muscle-	28 weeks including treatment period.	The VAS efficacy analysis reports scores for Week 0, 8, 16, and 28. The WA group reports VAS scores of 8.62, 4.93, 5.04, and 4.48 respective to time. The MS group reports	"In conclusion, there is as yet no consensus on which is the most effective exercise intervention to reduce pain. Our results revealed that both exercise	Data suggests comparable efficacy between MS and WA.

					control group is 46.1 years. The authors did not report sex.	Strengthening Exercises (MS) (n=30) – Patients followed exercise protocol of 11 free exercise. The intensity increased every 2 weeks. Vs. Control (n=30) – Patients did not engage in exercise.		VAS scores of 8.67, 5.62, 4.26, and 6.00 respective to time. The control group reports scores of 8.37, 6.41, 6.37, and 6.52 respective to time. Significant reduction in pain intensity in first 8 weeks, ($p<0.01$). Pain remained stable in control ($p=0.56$ and WA ($p=0.71$) after 8 weeks.	modalities (WA and MS) provided better pain relief in patients with Fibromyalgia than medication alone or conventional treatment, which is in agreement with other studies."	
Meeus M, 2015 (5.0)	Exercise	RCT	Sponsored by funded by ME Research UK. No COI.	N = 53 patients with either rheumatoid arthritis, chronic fatigue syndrome and fibromyalgia, or controls.	The mean age for the RA patients is 54.25 years. The mean age for the control group is 41.06 years. The mean age of the CFS/FM group is 44.58 years. 0 males, 53 females.	Paracetamol – Patients were given 1g paracetamol before exercise vs. Placebo – Patients were given 1g dextrose before exercise. (n=) was not specified by author.	No follow up.	The verbal numeric rating scale scores for patients with fibromyalgia in the finger was 5.16 before exercise and 5.00 after exercise. The VNRS in the shoulder was 4.64 before exercise and 5.11 after exercise.	"This study evaluates pain scores, TS, and CPM in response to submaximal exercise in 2 different chronic pain populations and healthy controls. In patients with RA, exercise had positive effects on TS, suggesting normal EIA. In patients with CFS/FM, these positive effects were only observed after paracetamol and	Crossover design. Single dose study only.

									results were inconsistent."	
Ang DC, 2013 (5.0)	Motivational Interviewing	RCT	Sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. No mention of COI.	N=216 patients with Fibromyalgia.	The mean age of the motivational interviewing group is 46 years. 4 males, 103 females. The mean age of the education control group is 45.7 years.	Motivational Interviewing (MI) (n=107) – received six telephone-delivered exercise-based MI sessions for a 12 week period. Vs. Education control (EC) (n=109) - received an equal number of telephone contacts to control for time and therapist attention.	Patients assessed at baseline, 12 weeks, 3 month follow up, and 6 month follow up.	The change is FIQ-physical impairment at 6 month follow up is -1.7 ($p<0.01$) for MI intervention group and -1.4 ($p<0.01$) for the education control group. P=0.39 MI vs. EC. The percent of subjects with ≥ 30-minute increment of MPVA (CHAMPS) at 6 month follow up is 54% MI intervention group and 52% education group. P=0.89.	"Despite a lack of benefits on long term outcome, MI appears to have short-term benefits with respect to self-report physical activity and clinical outcomes."	Data suggests some minor short term benefits but general lack of efficacy.
Mannerkorpi 2010 (4.5)	Aerobic Exercise	RCT	Supported by a grant from the Swedish Research Council. No COI.	N=67 patients with fibromyalgia by the American College of Rheumatology criteria (1990).	0 males, 67 females; Mean age in Nordic Walking group is 48±7.8 vs Low Intensive Walking group is 50±7.6.	Nordic Walking group (NW) (N=28) patients did 2, 20 minute session of moderate activity (>12 Rate of Perceived exertion (RPE)) for 15 weeks.	Follow up at baseline and 15 weeks.	6 min walking test improvement, baseline to post test, NW vs LIW: 37.7±41.8 vs 8.6±42.2 ($p=0.009$) effect size=0.69. Fibromyalgia impact questionnaire	"In conclusion, a supervised 15-week NW program designed to alternate between low and moderate-to-high exercise intensity, was found to be a feasible mode of	Data Suggest moderate-high intensity aerobic exercise via Nordic walking twice per week X 15 weeks improved function and

						vs Low intensity Walking control group (LIW) (N=26) participate in 1 exercise session a week for 15 weeks at low intensity (RPE of 9-11)		pain section did not change significantly between groups (p=0.626).	exercise for patients with FM. Most patients tolerated this mode of exercise, and pain severity did not change significantly over time during the exercise period. The participants in the NW program improved their functional capacity and decreased their level of activity limitations compared to active comparators."	acuity but did not change pain severity.
Rooks DS, 2007 (4.5)	Exercise	RCT	Sponsored by an Arthritis Foundation Investigator Award (Dr Rooks) and National Institutes of Health grants K23 AR48305 (Dr Rooks), RO3 AR047398 (Dr Rooks), K24 AR02123 (Dr Katz), P60 AR47782 (Dr	N = 207 patients with fibromyalgia.	The mean age of the AE group is 48 years. 0 males, 35 females. The mean age of the ST group is 50 years. 0 males, 35 females. The mean age of the FSHC group is 51 years. 0 males, 27 females.	AE (n=35) – Aerobic and Flexibility exercise. Vs. ST (n=35) – Strength training, aerobic, and flexibility exercise. Vs.	6 months.	The Self-efficacy scale for pain reported difference between pre and post intervention the following scores: AE – 9.8 ($p<0.01$ for within group changes) ($p<0.05$ between-group differences of change compared to education group). ST – 2.5	"Our findings suggest that appropriate exercise and patient education be included in the treatment of fibromyalgia."	Data suggests a combination of self-management education with exercise is the best treatment of fibromyalgia. Progressive walking and flexibility with or without strength training improves

			Iversen and Katz), and RR01032 (Dr Gautan). No COI.		The mean age of the ST-FSHC group is 50 years. 0 males, 38 females.	FSHC (n=27) – Fibromyalgia Self-Help Course. ST-FSHC (n=38) – Combination of strength training, aerobic, and flexibility exercise with the Fibromyalgia Self-Help Course.		(p<0.05 between-group differences of change compared to education group). FSHC - -11.0 (p<0.001 for within group changes). ST-FSHC – 7.6 (p<0.05 for within-group changes) (p<0.05 between-group differences of change compared to education group).		physical, emotional, and social functions.
Sañudo B, 2011 (4.5)	Exercise	RCT	No sponsorship or COI.	N = 42 patients with fibromyalgia.	The mean age of the exercise group is 55.48 years. 0 males, 18 females. The mean age of the control group is 56.15 years. 0 males, 20 females.	Exercise group (n=18) – Patients performed aerobic, strength, and flexibility exercise for 24 weeks. Vs. Control group (n=20) – usual care control	Follow up at baseline and 24 weeks.	The Fibromyalgia Impact Questionnaire (FIQ) score at baseline for exercise and control groups was 63.1 and 61.6, respectively. (p=0.761). The FIQ score at 24 weeks for exercise and control groups was 54.9 and 64.5, respectively. (p=0.027). The difference	"Results confirm that a long-term combination of aerobic exercise, strengthening and flexibility improves psychological health status and health-related quality of life in patients with fibromyalgia."	Usual care bias. Data suggests long term aerobic exercise, strengthening and flexibility in combination improves quality of life and physiological health in fibromyalgia patients.

								between the two groups from baseline to 24 weeks was d=0.58 (95% coincidence interval).		
Valim V, 2013 (4.5)	Exercise	Pilot Study	No sponsorship or COI.	N= 22 patients with fibromyalgia.	The mean age of the aerobic exercise group is 44 years. 0 males, 14 females. The mean age of the stretching exercise group is 47 years. 0 males, 8 females.	Aerobic exercise (n= 14) – Patients walked daily for 20 weeks. Vs. Stretching exercise (n= 8) – Patients performed mild stretches daily for 20 weeks.	Follow up at baseline and 20 weeks.	Levels of 5HT and 5HIAA changed significantly in the aerobic group (5HT: P = 0,03; 5HIAA: P = 0,003). No statistically significant change occurred in the stretching group.	"Aerobic training increases the 5HIAA and 5HT levels and it could explain why aerobic exercise can improve symptoms in fibromyalgia syndrome patient more than stretching exercise."	Pilot study. Data suggests aerobic exercise increases 5HIAA and 5HT where stretching only slightly increase the above metabolites.
Valim 2003 (4.0)	Aerobic Exercise	RCT	Sponsored by FAPESP (Research support fund of the state of Sao Paulo). No mention of COI.	N=67 patients diagnosed with fibromyalgia by the American College of Rheumatology criteria (1990).	0 males, 67 females; mean age 46.05±9.82.	Aerobic group (AE) (N=32) participated in a walking program with frequency meters and physiotherapists 3 times a week for 45 minutes. vs Stretching group (SE) (N=28) participated in 3 sessions of 45 minutes a	Follow up at baseline, 10, and 20 weeks.	Fibromyalgia Impact score, at wk 10 - 20, AE vs SE: 3.73±2.22 - 3.04±1.92 vs 4.09±1.83 - 4.03±1.55 (p=0.049). Beck Depression inventor (BDI), wk 0 – 10, AE vs SE: 19.90±7.88 - 14.00±7.89 vs 13.89±7.89 – 13.56±10.26 (p=0.017). Pain score wk 0 – 10, AE vs SE: 23.57±8.8 –	"The main finding in this study is that aerobic exercise improves the quality of life when compared to another control physical intervention (stretching) in patients with FM."	Data suggest greater improvement in aerobic group vs stretching. However, the fitness gains were unrelated to FM symptom improvement.

						week. Included 17 exercises that stretched all major muscle groups.		21.29±8.73 vs 23.43±8.49 – 27.63±10.09 (p=0.027).		
Kaleth 2014 (4.0)	Aerobic Exercise	RCT	Sponsored by a grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. No COI.	N=199 patients diagnosed with fibromyalgia by the American College of Rheumatology criteria (1990).	10 males, 189 females; mean age of 46±11.3.	Motivational Interviewing (MI) (N=?) Patients received 2 sessions of supervised exercise and then motivation interviews while continuing regimen for 36 weeks. vs Outcome health education (AC) (N=?) Patients received 2 sessions of supervised exercise and then telephone education while continuing regimen for 36 wks.	Follow up at baseline and week 12, 24, and 36.	Multivariate regression for every 1,000 steps/day, (beta change at wk 12, p-value) for variables Fibromyalgia impact questionnaire (FIQ), FIQ-physical impairment, Brief Pain inventory (BPI interferences, Physical Health Questionnaire (PHQ-8), Short form- 36 (SF-36): FIQ-PI -0.33 (p=0.004), BPI -0.27 (p=0.0179), PHQ-8 -0.60 (p=0.0301), SF-36 2.21 (p=0.0169).	"[A]n exercise prescription that includes recommendations to gradually accumulate at least 5,000 additional steps per day may result in clinically significant improvements in outcomes relevant to patients with FM."	Secondary Analysis. Data suggest increasing step counts (at least 5,000 extra step counts a day) may lead to significant positive benefits in Fibromyalgia patients.
Costa DD, 2005 (4.0)	Exercise	RCT	Sponsored by The Arthritis Society. No COI.	N = 79 patients with fibromyalgia	The mean age of the exercise group is	Exercise group (n=39) – Patients met 4 times with the	Follow up at baseline, 12 weeks,	The FIQ score post-treatment for the exercise and control	"Home-based exercise, a relatively low-cost treatment	Data suggest home based exercise group had

					49.2 years. 0 males, 39 females. The mean age of the control group is 52.3 years. 0 males, 40 females.	same exercise physiologist. Vs Control group (n=40) – Patients were asked to complete a FM symptom measure and to record exercise activity weekly during 12 weeks.	3 months and 9 months.	group was -10.1 and -2.8, respectively. (p=0.078). The FIQ score 3 months post treatment was -7.8 exercise and -0.04 control. (p=0.053). The FIQ score 9 months post treatment was -10.1 exercise and -0.024 control. (p=0.009).	modality, has the potential to improve important health outcomes in FM."	statistically significant improvement in upper body pain at both 3 and 9 months post intervention.
Redondo JR, 2003 (4.0)	Exercise	RCT	No mention of sponsorship or COI.	N = 56 patients with fibromyalgia.	0 males, 56 females. Author does not report age.	PE group (n=19) – Physical exercise. Patients underwent 45 mins session of PE 5 times weekly. Vs. CBT group (n = 21) – Cognitive behavioral therapy. CBT was mainly designed for reducing distorted pain dimensions, to cope with chronic pain,	Follow up at baseline, post treatment, 6 months and 1 year.	The total FIQ scores for the PE group are 52.0 baseline, 40.8 posttreatment, 48.0 6 month, and 47.7 1 year. The total FIQ scores for the CBT group are 52.0 baseline. 44.3 posttreatment, 47.4 6 months, and 47.8 1 year.	"PE and CBT improve clinical manifestations in FM patients only for short periods of time. Improvement in self-efficacy and physical fitness are not associated with improvement in clinical manifestations."	Data suggests short term comparable efficacy between both the exercise and CBT groups but at one year follow up, gains returned to baseline with the exception of the functional capacity in the exercise group.

						and to increase self-efficacy, following techniques previously described for the management of chronic pain.				

Evidence for Strengthening, Stabilization, and Resistance Exercises

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Palstam, 2016 (6.5)	Fear Avoidance	Sub-study of RCT	Supported by Swedish Rheumatism Association. No COI.	N = 67 patients with Fibromyalgia.	Mean age: 51 Sex(M:F) 0:67	Participants completed a 15 week intervention consisting of performing progressive resistance exercise twice a week.	15 weeks.	Improvement in pain disability was explained 28% (p=0.005) by high pain disability at baseline, and improvement in fear avoidance beliefs. High baseline scores and improvement in fear avoidance explained the Improvement in recreation and social activity by 32% (p=0.0025) and 30% (p=0.017) respectively.	"The reduced pain disability seemed to be mediated by decreased fear avoidance beliefs."	Sub study of original RCT (secondary analysis). Data suggest a decrease of fear avoidance beliefs after person-centered progressive resistance exercise is associated with a reduction in pain disability in fibromyalgia women.
Ericsson A 2016 (6.5)	Fibromyalgia	RCT	The study was supported by the Swedish Rheumatism Association, the	N = 130 females with fibromyalgia	Age range 20–65 years; all females.	The effects of person-centered progressive resistance exercise (n=67) Vs.	Post-treatment examination after 15 weeks.	A higher improvement was found at the post-treatment examination for change in the	"The present study is the first to show that person centered progressive resistance	Data suggest marked improvement in sleep efficiency and physical fatigue (resistance

			Swedish Research Council, the Health and Medical Care Executive Board of Västra Götaland Region, ALF-LUA at Sahlgrenska University Hospital, Stockholm and Östergötland County Councils (ALF), and AFA Insurance and Gothenburg Center for Person Centered Care (GPCC). The authors declare no conflicts of interest.			An active control group (n=63). The intervention was performed twice a week for 15 weeks.		resistance exercise group, as compared to change in the active control group in the MFI-20 subscale of physical fatigue (resistance group Δ –1.7, SD 4.3, controls Δ 0.0, SD 2.7, p = 0.013), with an effect size of 0.33. Sleep efficiency was the strongest predictor of change in the MFI-20 subscale general fatigue (beta = −0.54, p = 0.031, R^2 = 0.05). Participating in resistance exercise (beta = 1.90, p = 0.010) and working fewer hours per week (beta = 0.84, p = 0.005) were	exercise contributed to improvement in physical fatigue in women with FM. Aspects of work and sleep were found to contribute to the improvement in fatigue."	vs relaxation)

								independent significant predictors of change in physical fatigue (R^2 = 0.14).		
Haanen, 1991 (Score=6.5)	Strengthening/Stabilization	RCT	No mention of sponsorship or COI.	N = 40 with "refractory" fibromyalgia.	Mean age: 45.05 years; 2 males, 38 females.	Hypnotherapy (n=20) – patients recived hypnotherapy of 8 1-hour sessing in decreasing frequency over a 3 month period. vs. Physical therapy (n=20) – patients received physical therapy, massage and training in muscle relaxation, 1 to 2 hours a week for 12 weeks.	24 weeks.	VAS pain ratings at baseline tended higher in hypnotherapy group (7.0 vs. 6.2, p = 0.2). Muscle pain VAS ratings (baseline/12 weeks/24 weeks): PT (9.5/9.3/8.8) vs. hypnotherapy (9.3/6.0/7.1, p <0.05). Physician blinded assessments: PT (6.2/8.0/7.9) vs. hypnotherapy (7.0/7.0/7.4).	"Hypnotherapy seems to be effective in relieving complaints in some patients with refractory fibromyalgia. In professional hands it is a safe and inexpensive mode of treatment."	As patients already had prior PT, study appears biased in favor of hypnotherapy through assigning patients to "more of the same."
Larsson A 2015 (6.0)	Fibromyalgia	RCT	No COI. The study was supported by the Swedish	N=130 women with fibromyalgia	Mean age: 51.5 years; all females.	Resistance exercise (experimental) (n = 67) Vs. Relaxation	13-18 months	Significant improvements were found for isometric knee-extension	"Person-centered progressive resistance exercise was shown to be a	Data suggest person centered progressive resistance exercise

			Rheumatism Association, the Swedish Research Council, the Health and Medical Care Executive Board of Västra Götaland Region, ALF-LUA at Sahlgrenska University Hospital, Stockholm County Council (ALF), The Norrbacka-Eugenia foundation, and Gothenburg Center for Person Centered Care (GPCC)			therapy (control) (n = 63)		force (p = 0.010), health status (p = 0.038), current pain intensity (p = 0.033), 6MWT (p = 0.003), isometric elbow flexion force (p = 0.02), pain disability (p = 0.005), and pain acceptance (p = 0.043) in the resistance exercise group (n = 56) when compared to the control group (n = 49). PGIC differed significantly (p = 0.001) in favor of the resistance exercise group at post-treatment examinations. No significant differences between the resistance	feasible mode of exercise for women with FM, improving muscle function, health status, current pain intensity, pain management and participation in activities of daily life. At long-term follow up the effects had declined to baseline levels, implying that a longer period of guidance and support is recommended to increase the possibilities of maintaining regular exercise habits."	improved fatigue and muscle strength in FM women and pain intensity immediately after exercise. Data suggest significant short term improvement from progressive resistance exercise in terms of knee extension force elbow flexion force pain disability, pain acceptance and pain intensity compared to controls but at 13-18 month there were no significant differences between groups.

								exercise group and the active control group were found regarding change in self-reported questionnaires from baseline to 13–18 months		
Hooten 2012 (5.5)	Aerobic Exercise	RCT	Sponsored by a CR-20 grant from the Mayo foundation. No COI.	N=72 patients diagnosed with fibromyalgia using American College of Rheumatology criteria.	7 males, 65 females; Mean age of aerobic group is 45.8±11.5 and strength group is 47.3±10.1.	Strength Training Group (N=36) upper and lower main muscle group strength exercises were performed daily for 25-30 minutes under supervision of Physical therapist. vs Aerobic Training group (N=36) patients used a stationary bicycle to eventually get to 70% max HR.	Baseline and week 3.	Mean Pain severity change at week 3, intention to treat analysis, Aerobic group and strength group: 11.0 (95% CI 6.4 - 15.6) and 12.0 (95% CI 7.0 - 17.0). No significant difference in between groups for pain severity in fibromyalgia.	"This study found that strength and aerobic exercise had equivalent effects on reducing the pain severity among patients with fibromyalgia."	Data suggest comparable efficacy between aerobic vs strengthening exercises on pain severity.

Kingsley JD 2005 (5.5)	Fibromyalgia	RCT	Supported by Florida State University Council for Faculty Research– First Year Assistant Professor Program and supported in kind by the Tallahassee Communicare Wellness Center. No COI.	N= 29 women with fibromyalgia	Mean age: 46.2 years; all females.	Control (n=14; wait-listed for exercise) vs. strength (n=15) group. After the first 4 weeks, 7 (47%) women dropped from the strength group. Total 12 week intervention	No follow up mentioned	The strength group significantly (*P*≤.05) improved upper- (strength, 39±11 to 42±12kg; control, 38±13 to 38±12kg) and lower- (strength, 68±28 to 82±25kg; control, 61±25 to 61±26kg) body strength. Upper-body functionality measured by the Continuous-Scale Physical Functional Performance test improved significantly (strength, 44±11 to 50±16U; control, 51±11 to 49±13U) after training. Tender point sensitivity and	The 12-week progressive strength-training program not only significantly increased strength but also increased selected components of functionality. This program did not exacerbate fibromyalgia symptoms in the women who completed the study and did not result in musculoskeletal damage or injury. The women improved strength and functionality of routine tasks of daily living with 1 set of 8 to 12 repetitions of 11 exercises that worked the major muscle groups of the body,	Waitlist control bias. Data suggest strength training improved strength in FM patients.

								fibromyalgia impact did not change.	performed twice a week at an intensity of 60% to 80% of initial 1-RMs.	
Kayo A, 2012 (5.5)	Exercise	RCT	No sponsorship or COI.	N = 90 patients with fibromyalgia.	The mean age of the WA group was 47.7 years. The mean age of the MS group was 46.7 years. The mean age of the control group is 46.1 years. The authors did not report sex.	Walking Program (WA) (n=30) – patients walked every day for 25 to 40 mins. The intensity increased every 4 weeks. Vs. Muscle-Strengthening Exercises (MS) (n=30) – Patients followed exercise protocol of 11 free exercise. The intensity increased every 2 weeks. Vs. Control (n=30) – Patients did not engage in exercise.	28 weeks including treatment period.	The VAS efficacy analysis reports scores for Week 0, 8, 16, and 28. The WA group reports VAS scores of 8.62, 4.93, 5.04, and 4.48 respective to time. The MS group reports VAS scores of 8.67, 5.62, 4.26, and 6.00 respective to time. The control group reports scores of 8.37, 6.41, 6.37, and 6.52 respective to time. Significant reduction in pain intensity in first 8 weeks, ($p<0.01$). Pain	"In conclusion, there is as yet no consensus on which is the most effective exercise intervention to reduce pain. Our results revealed that both exercise modalities (WA and MS) provided better pain relief in patients with Fibromyalgia than medication alone or conventional treatment, which is in agreement with other studies."	Data suggests comparable efficacy between MS and WA.

								remained stable in control (p=0.56 and WA (p=0.71) after 8 weeks.		
Paolucci, T 2015 (5.0)	Proprioceptive Rehabilitation	RCT	No sponsorship or COI.	N=62 patients with fibromyalgia.	The mean age of the PS group is 49.3 years. 0 males, 20 females. The mean age of the PE group is 50.4 years. 0 males, 21 females. The mean age of the control group is 51.3 years. 0 males, 21 females.	Perceptual surfaces (PS) Group (n=20) – Patients received a therapeutic approach based on the interaction between the patient's back or painful area and a support surface. Vs. Physical exercises (PE group (n=21) - received a conventional treatment based on a program comprising 10 1-hour sessions, held twice a week	At baseline (T0), 5 weeks (T1), and 12 week (T2) follow up period.	The FIQ score respective to T0, T1, and T2 for PS group are 68.0 ± 13.0, 56.0 ± 13.0, 55.0 ± 14.0, p<0.001. For PE Group: 66.0 ± 13.0, 54.0 ± 10.0, 54.0 ± 11.0, p=0.003. For CG: 64.0 ± 9.0, 66.0 ± 10.0, 66.0 ± 10.0, p=0.002.	"Perceptual surfaces are efficacious in treating female patients with FM, similar to physical group exercises, improving physical function and mitigating pain."	Data suggests perceptual surfaces group experienced reduced pain vs other 2 groups.

						Vs. Control Group (n=21) – Patients received an education session on fibromyalgia. Patients were to perform exercise taught at education session at least 1 hour 2 times a week.				
Jones, 2008 (5.0)	Pyridostigmine and Exercise	RCT	Supported by the National Institute of Nursing Research Grant. COI, Dr. Jones has received fees (less than $10,000) for service on the Speaker's Bureau for Pfizer. Dr. Bennett has received speaking fees (less than	N = 165 patients with Fibromyalgia	Mean age 49.45±8.05 Sex(M:F) 5:160	Placebo group with Diet recall but No exercise were asked to complete a monthly log of food intake. (N = 41) vs Placebo group, Group Exercise completed 60min group exercise classes 3x a week for 6 months.	6 months	Interaction of PYD and training exercise (F [1,143] = 0.04, (P = 0.849)), main effect of PYD (F [1,143] = 0.97, (P = 0.325)), and main effect of exercise (F [1,143] = 2.39, (P = 0.124)) all failed to reach significance.	"Neither the combination of PYD plus supervised exercise nor either treatment alone yielded improvement in most FM symptoms."	Data suggest that although PYD improved anxiety, sleep, exercise frequency (which improved fatigue and fitness), PYD alone or in combination with exercise did not improve most FM associated symptoms.

			$10,000 each) from Eli Lilly, Pfizer, and Grünenthal.			(N = 39) Pyridostigmine (PYD(, with Diet recall but No group exercise (N=42) received PYD Bromide (180mg/day) for 6 months and asked to keep a monthly log of food intake Vs. Pyridostigmine with Group exercise received PYD bromide (180mg/day) for 6months and completed 60min group exercise classes 3x a week for 6 months. (N=43)				
Jones KD 2002 (4.5)	Fibromyalgia	RCT	Supported by an Individual National Research Service Award (#1F31	N= 56 patients with fibromyalgia	Mean age: 48.1 years; all women.	Treatment group (n=28) Vs. Control group (n=28) to receive a twice weekly program of	No follow up period mentioned	No statistically significant differences between groups were found on independent	"This study reports that female patients with FM can engage in a specially tailored muscle	Data suggest both groups showed improvement in FM symptoms but the

			NR07337-01A1) from the National Institutes of Health, a doctoral dissertation Grant (#2324938) from the Arthritis Foundation, and funds from the Oregon Fibromyalgia Foundation.			either muscle strengthening for 12 weeks or stretching for 12 weeks		t tests. Paired t tests revealed twice the number of significant improvements in the strengthening group compared to the stretching group. Effect size scores indicated that the magnitude of change was generally greater in the strengthening group than the stretching group.	strengthening program and experience improvements in strength and overall disease activity, without a significant exercise induced flare in pain or increased reliance on pain medications. Flexibility training alone also resulted in overall improvements, albeit of a lesser degree."	strengthening group was a little better than the flexibility group.
Sañudo B, 2011 (4.5)	Exercise	RCT	No sponsorship or COI.	N = 42 patients with fibromyalgia.	The mean age of the exercise group is 55.48 years. 0 males, 18 females. The mean age of the control group is 56.15 years. 0 males, 20 females.	Exercise group (n=18) – Patients performed aerobic, strength, and flexibility exercise for 24 weeks. Vs. Control group (n=20) – usual care control	Follow up at baseline and 24 weeks.	The Fibromyalgia Impact Questionnaire (FIQ) score at baseline for exercise and control groups was 63.1 and 61.6, respectively. (p=0.761). The FIQ score at 24 weeks for exercise and control groups was	"Results confirm that a long-term combination of aerobic exercise, strengthening and flexibility improves psychological health status and health-related quality of life in patients with fibromyalgia."	Usual care bias. Data suggests long term aerobic exercise, strengthening and flexibility in combination improves quality of life and physiological health in fibromyalgia patients.

								54.9 and 64.5, respectively. (p=0.027). The difference between the two groups from baseline to 24 weeks was d=0.58 (95% coincidence interval).		
Kibar S 2015 (4.0)	Fibromyalgia	RCT	NO mention of industry sponsorship or COI.	N = 57 patients with fibromyalgia	Mean age: 48.13 years	Group 1: flexibility and balance exercises (N =28) Vs Group 2 Only a flexibility program (N =29)	For 6 weeks.	In group 1, statistically significant improvements were observed in all parameters (P<.05), but no improvement was seen in group 2 (P>.05). When comparing the 2 groups, there were significant differences in group 1 concerning the KAT static balance test (P=.017) and FIQ measurements (P=.005). In	In this study, the 6-week balance training program had a beneficial effect on static balance and functional levels of patients with FMS. In addition, we determined that deterioration of depression and higher BMI were related to the balance deficit and fall risk. Our findings indicate that a balance assessment should be performed	Data suggests balance training had a posture effect on improving depression and balance

								the correlation analysis, the BDI was correlated with the BBS (r=-.434) and Hendrich II results (r=.357), whereas body mass index (BMI) was correlated with the KAT static balance measurements (r=.433), BBS (r=-.285), and fall frequency (r=.328).	during the first evaluation of these patients and balance training should be included in the treatment protocols of FMS patients with balance disorders. Our study only presents preliminary results regarding the effectiveness of balance exercises on FMS. Therefore, we recommend that further studies be conducted to determine whether balance training can improve postural stability and reduce falls in FMS. We hope that our findings provide the impetus for a definitive randomized trial in the future.	

Redondo JR, 2003 (4.0)	Exercise	RCT	No mention of sponsorship or COI.	N = 56 patients with fibromyalgia.	0 males, 56 females. Author does not report age.	PE group (n=19) – Physical exercise. Patients underwent 45 mins session of PE 5 times weekly. Vs. CBT group (n = 21) – Cognitive behavioral therapy. CBT was mainly designed for reducing distorted pain dimensions, to cope with chronic pain, and to increase self-efficacy, following techniques previously described for the management of chronic pain.	Follow up at baseline, post treatment, 6 months and 1 year.	The total FIQ scores for the PE group are 52.0 baseline, 40.8 posttreatment, 48.0 6 month, and 47.7 1 year. The total FIQ scores for the CBT group are 52.0 baseline. 44.3 posttreatment, 47.4 6 months, and 47.8 1 year.	"PE and CBT improve clinical manifestations in FM patients only for short periods of time. Improvement in self-efficacy and physical fitness are not associated with improvement in clinical manifestations."	Data suggests short term comparable efficacy between both the exercise and CBT groups but at one year follow up, gains returned to baseline with the exception of the functional capacity in the exercise group.
Jones 2007 (4.0)	Pyridostigmine and Exercise	RCT	No mention of sponsorship or COI.	N = 165 patients with Fibromyalgia	Mean age 49.45±8.05	Placebo group with Diet recall but No	6 months	PYD did not significantly increase Insulin Like	"A combination of triweekly supervised	High dropout rate. Data

					Sex(M:F) 5:160	exercise were asked to complete a monthly log of food intake. (N = 41) vs Placebo group, Group Exercise completed 60min group exercise classes 3x a week for 6 months. (N = 39) Pyridostigmine (PYD(, with Diet recall but No group exercise (N=42) received PYD Bromide (180mg/day) for 6 months and asked to keep a monthly log of food intake Vs. Pyridostigmine with Group exercise received PYD		Growth Factor-I (IGF-I) during exercise classes. Interaction of PYD and exercise classes for IGF-I (F (1,147) = 0.02, (p = 0.891)).	exercise plus the daily use of PYD for 6 months failed to increased IGF-I levels in patients with FM, despite the confirmation that PYD normalizes the acute GH response to strenuous aerobic exercise."	suggest lack of efficacy.

						bromide (180mg/day) for 6months and completed 60min group exercise classes 3x a week for 6 months. (N=43				

Evidence for Stretching Exercises (Non-Yoga)

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Sañudo 2010 (5.5)	Aerobic Exercise	RCT	Sponsored by the University of Seville. No COI.	N=64 patients diagnosed with fibromyalgia using American College of Rheumatology criteria.	0 males, 64 females; Mean age in AE group 55.9±1.6, CE group 55.9±1.7, and control group 56.6±1.9.	Aerobic Exercise Group (AE) (N=22) which did 2 weekly sessions of 45-60 minutes. Vs Combined Exercise group (CE) (N=21) Did AE sessions for 15-20 minutes and combined with muscles strengthening exercises vs control group (control) (N=21) typical medical treatment and no	Follow up at baseline and 24 weeks.	Fibromyalgia Impact Questionnaire (FIQ) score improvement, baseline vs 24 wks, AE & CE: 8.8±14 & 8.8±12 (p<0.20). Beck Depression inventory (BDI) improvement baseline to 24 wks, AE and CE: 8.5±8 (p<0.001) & 6.4±4 (p<0.001). SF-36 score improvement, baseline to 24 wks, AE and CE: 8.9±10 & 8.4±11	"Given the equivalent time commitment required for the AE and CE interventions, our results suggest that women with a diagnosis of FMS can gain additional health benefits by engaging in combined supervised strength, flexibility, and aerobic exercise."	Usual Care Bias. Unclear if FM participants had different length of time since diagnosis of fibromyalgia. Data suggest both exercise groups improved.

						deviation from normal daily routines.		(p<0.01). CE hand strength better than controls (p<0.012). Generally greater effect size differences were observed in the CE group.		
Sañudo B, 2011 (4.5)	Exercise	RCT	No sponsorship or COI.	N = 42 patients with fibromyalgia.	The mean age of the exercise group is 55.48 years. 0 males, 18 females. The mean age of the control group is 56.15 years. 0 males, 20 females.	Exercise group (n=18) – Patients performed aerobic, strength, and flexibility exercise for 24 weeks. Vs. Control group (n=20) – usual care control	Follow up at baseline and 24 weeks.	The Fibromyalgia Impact Questionnaire (FIQ) score at baseline for exercise and control groups was 63.1 and 61.6, respectively. (p=0.761). The FIQ score at 24 weeks for exercise and control groups was 54.9 and 64.5, respectively. (p=0.027). The difference between the two groups from baseline to 24 weeks was d=0.58 (95% coincidence interval).	"Results confirm that a long-term combination of aerobic exercise, strengthening and flexibility improves psychological health status and health-related quality of life in patients with fibromyalgia."	Usual care bias. Data suggests long term aerobic exercise, strengthening and flexibility in combination improves quality of life and physiological health in fibromyalgia patients.

Rooks DS, 2007 (4.5)	Exercise	RCT	Sponsored by an Arthritis Foundation Investigator Award (Dr Rooks) and National Institutes of Health grants K23 AR48305 (Dr Rooks), RO3 AR047398 (Dr Rooks), K24 AR02123 (Dr Katz), P60 AR47782 (Dr Iversen and Katz), and RR01032 (Dr Gautan). No COI.	N = 207 patients with fibromyalgia.	The mean age of the AE group is 48 years. 0 males, 35 females. The mean age of the ST group is 50 years. 0 males, 35 females. The mean age of the FSHC group is 51 years. 0 males, 27 females. The mean age of the ST-FSHC group is 50 years. 0 males, 38 females.	AE (n=35) – Aerobic and Flexibility exercise. Vs. ST (n=35) – Strength training, aerobic, and flexibility exercise. Vs. FSHC (n=27) – Fibromyalgia Self-Help Course. ST-FSHC (n=38) – Combination of strength training, aerobic, and flexibility exercise with the Fibromyalgia Self-Help Course.	6 months.	The Self-efficacy scale for pain reported difference between pre and post intervention the following scores: AE – 9.8 ($p<0.01$ for within group changes) ($p<0.05$ between-group differences of change compared to education group). ST – 2.5 ($p<0.05$ between-group differences of change compared to education group). FSHC - -11.0 ($p<0.001$ for within group changes). ST-FSHC – 7.6 ($p<0.05$ for within-group changes) ($p<0.05$ between-group differences of change	"Our findings suggest that appropriate exercise and patient education be included in the treatment of fibromyalgia."	Data suggests a combination of self-management education with exercise is the best treatment of fibromyalgia. Progressive walking and flexibility with or without strength training improves physical, emotional, and social functions.

								compared to education group).		
Valim V, 2013 (4.5)	Exercise	Pilot Study	No sponsorship or COI.	N= 22 patients with fibromyalgia.	The mean age of the aerobic exercise group is 44 years. 0 males, 14 females. The mean age of the stretching exercise group is 47 years. 0 males, 8 females.	Aerobic exercise (n= 14) – Patients walked daily for 20 weeks. Vs. Stretching exercise (n= 8) – Patients performed mild stretches daily for 20 weeks.	Follow up at baseline and 20 weeks.	Levels of 5HT and 5HIAA changed significantly in the aerobic group (5HT: P = 0,03; 5HIAA: P = 0,003). No statistically significant change occurred in the stretching group.	"Aerobic training increases the 5HIAA and 5HT levels and it could explain why aerobic exercise can improve symptoms in fibromyalgia syndrome patient more than stretching exercise."	Pilot study. Data suggests aerobic exercise increases 5HIAA and 5HT where stretching only slightly increase the above metabolites.
Kibar S 2015 (4.0)	Fibromyalgia	RCT	NO mention of industry sponsorship or COI.	N = 57 patients with fibromyalgia	Mean age: 48.13 years	Group 1: flexibility and balance exercises (N =28) Vs Group 2 Only a flexibility program (N =29)	For 6 weeks.	In group 1, statistically significant improvements were observed in all parameters (P<.05), but no improvement was seen in group 2 (P>.05). When comparing the 2 groups, there were significant differences in group 1 concerning the	In this study, the 6-week balance training program had a beneficial effect on static balance and functional levels of patients with FMS. In addition, we determined that deterioration of depression and higher BMI were related to the balance deficit and fall risk. Our	Data suggests balance training had a posture effect on improving depression and balance

								KAT static balance test (P=.017) and FIQ measurements (P=.005). In the correlation analysis, the BDI was correlated with the BBS (r=-.434) and Hendrich II results (r=.357), whereas body mass index (BMI) was correlated with the KAT static balance measurements (r=.433), BBS (r=-.285), and fall frequency (r=.328).	findings indicate that a balance assessment should be performed during the first evaluation of these patients and balance training should be included in the treatment protocols of FMS patients with balance disorders. Our study only presents preliminary results regarding the effectiveness of balance exercises on FMS. Therefore, we recommend that further studies be conducted to determine whether balance training can improve postural stability and reduce falls in FMS. We hope that our findings provide the	

									impetus for a definitive randomized trial in the future.	
Redondo JR, 2003 (4.0)	Exercise	RCT	No mention of sponsorship or COI.	N = 56 patients with fibromyalgia.	0 males, 56 females. Author does not report age.	PE group (n=19) – Physical exercise. Patients underwent 45 mins session of PE 5 times weekly. Vs. CBT group (n = 21) – Cognitive behavioral therapy. CBT was mainly designed for reducing distorted pain dimensions, to cope with chronic pain, and to increase self-efficacy, following techniques previously described for the management of chronic pain.	Follow up at baseline, post treatment, 6 months and 1 year.	The total FIQ scores for the PE group are 52.0 baseline, 40.8 posttreatment, 48.0 6 month, and 47.7 1 year. The total FIQ scores for the CBT group are 52.0 baseline. 44.3 posttreatment, 47.4 6 months, and 47.8 1 year.	"PE and CBT improve clinical manifestations in FM patients only for short periods of time. Improvement in self-efficacy and physical fitness are not associated with improvement in clinical manifestations."	Data suggests short term comparable efficacy between both the exercise and CBT groups but at one year follow up, gains returned to baseline with the exception of the functional capacity in the exercise group.

Evidence for Exercise

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
McCain 1988 RCT	6.5	N = 42 with primary FM	20-week program of cardiovascular fitness (CVR) vs. flexibility exercises (FLEX)	Fitness training resulted in improved peak work capacity scores (+168.7± 166.8 vs. -7.3±7.9 kilopond-meters, p <0.001), as well as reduced pain threshold scores for palpation (p = 0.04). Nine patients (50%) in cardiovascular fitness group felt they moderately or markedly improved vs. two (11.1%) in flexibility exercises. Physician assessments of moderate or marked improvement 35% vs. 5.6%.	"Patients with primary fibromyalgia who achieve enhanced cardiovascular fitness after strenuous physical activity have modest improvements in both subjective and objective measurements of pain."	Blinding of exercises attempted between two patient groups, but effective blinding seems somewhat dubious. Baseline differences included younger age and higher pain intensity scores among cardiovascular fitness group.
Haanen 1991 RCT	6.5	N = 40 with "refractory" FM, most patients (n = 25) either in-capacitated or unemployed	Hypnotherapy vs. physical therapy for 12 weeks.	VAS pain ratings at baseline tended higher in hypnotherapy group (7.0 vs. 6.2, p = 0.2). Muscle pain VAS ratings (baseline/12 weeks/24 weeks): PT (9.5/9.3/8.8) vs. hypnotherapy (9.3/6.0/7.1, p <0.05). Physician blinded assessments: PT (6.2/8.0/7.9) vs. hypnotherapy (7.0/7.0/7.4).	"Hypnotherapy seems to be effective in relieving complaints in some patients with refractory fibromyalgia. In professional hands it is a safe and inexpensive mode of treatment."	As patients already had prior PT, study appears biased in favor of hypnotherapy through assigning patients to "more of the same."
Rooks 2007 RCT	6.5	N = 207 females with FM (ACR criteria used)	1) Aerobic and flexibility exercise vs. 2) strength training, aerobic and flexibility exercise vs. 3) Fibromyalgia Self-Help Course vs. 4)	Most pain and functional measures trended to be superior in aerobic exercise group with exception of FIQ score and chest and leg press values. However, psychosocial scores tended to be better in combined strength	"Progressive walking, simple strength training movements, and stretching activities improve functional status, key symptoms, and self-efficacy in women with fibromyalgia actively being treated with medication."	Study included exercise as adjunct to medication, thus models a study that addresses role of adjunctive therapy. Medical management not structured or well described. Study combined some exercises without including

			combination of strength training, aerobic and flexibility exercise and the self-help course for 16 weeks.	training/educational group. Dropout rates high (31%-46%), with patients dropping from self-help group due to dissatisfaction with assignment.		optimal combinations, thus utility for development of guidance somewhat reduced. Study demonstrates aerobic and strengthening exercises more important than education for treatment of fibromyalgia. Authors suggest both aerobic and strengthening effective treatments (which suggests may be synergistic benefits between aerobic and strengthening exercises).
van Santen 2002 RCT	6.0	N = 143 females with FM	Fitness program vs. biofeedback training vs. controls. Subjects additionally randomized by center to an additional educational program of 6x90 minute health promotion sessions over 24 weeks aimed at improving compliance.	VAS pain scores (baseline/change at 24 weeks): fitness [66.8±15.3/ -5.5 (95% CI -10.9 to -0.1)] vs. biofeedback [59.1±18.5/ -0.6 (-6.5 to 5.3)] vs. control [62.4±20.5/1.3 (-4.5 to 7.1)]. Physical fitness scores in Watts inexplicably somewhat favored controls then biofeedback then fitness group. General fatigue scores favored fitness group.	"In terms of training intensity and maximal heart rates, the high impact fitness intervention had a low impact benefit. Therefore effectiveness of high impact physical fitness training cannot be demonstrated. Thus compared to usual care, the fitness training (i.e., low impact) and biofeedback training had no clear beneficial effects on objective or subjective patient outcomes in patients with FM."	Baseline differences of longer disease duration at baseline in controls presumably biased against that group, but better physical condition in control group and somewhat higher pain ratings in fitness group at baseline may have biased in favor of control. In contrast with conclusions, data document only significant pain reductions occurred in fitness group, although ANOVA between-group differences not significant. Data suggest biofeedback trended towards more benefit than control treatment.
Schacter 2003 RCT	5.5	N = 143 sedentary females with FM	No exercise vs. 30-minute bout vs. 2 15-minute bouts of aerobic exercise a day. Programs designed to include videotapes. Researchers	FIQ total scores (baseline/post-test): no exercise group (5.5±1.3/ 5.4±1.6) vs. short bouts (5.4±1.5/5.2±1.8) vs. long bout (5.6±1.4/ 5.1±1.7). Blinded physician ratings of global severity were:	"Progressive, home-based, low-impact aerobics improved physical function and fibromyalgia symptoms minimally in participants who completed at least two thirds of the recommended exercise. Fractionation of exercise training provided no advantage in terms of	Dropout rates high, with 14% in no-exercise group vs. 38% in short bout and 29% in long bout groups.

			contacted subjects to encourage participation and work through barriers to compliance.	no exercise (5.3±1.6/ 4.8±1.6) vs. short bouts (4.9±1.7/4.2±1.7) vs. long bout (5.1±1.7/ 4.4±1.8). VAS pain ratings: no exercise (6.1±2.0/5.6±2.2) vs. short bouts (5.7±2.3/ 5.8±2.5) vs. long bout (5.8±1.8/5.3±2.3).	exercise adherence, improvements in fibromyalgia symptoms or physical function. High attrition rates and problems with exercise adherence were experienced in both exercise groups."	
King 2002 RCT	5.5	N = 152 females with FM (ACR criteria used)	Exercise-only vs. education-only vs. combined treatment vs. control group for 12 weeks. Control group received instructions on basic stretches and 5 items on general coping strategies.	Baseline data suggest exercise group less likely to be compensated (15.2/35.4/32.4/41.0%), somewhat less likely to be on anti-depressants (52.2/72.9/64.9/41.0%). FIQ scores (baseline/post test): exercise (52.4± 12.7/49.6±14.7) vs. education (56.8±10.7/ 54.0±14.8) vs. combination (52.9±10.7/ 44.7±18.6) vs. control (55.2±11.8/54.3±12.6). Six-minute walk results (baseline/post treatment/follow-up): exercise (491.4/525.5/ 520.9) vs. education (495.4/494.3/476.6) vs. combination (452.0/ 501.1/465.2) vs. control (494.6/498.7/479.4).	"Subjects receiving the combination of exercise and education and who complied with the treatment protocol improved their perceived ability to cope with other symptoms. In addition, a supervised exercise program increased walking distance at post-test, an increase that was maintained at follow up in the exercise-only group."	Estimated that most subjects were at 60-75% of their heart rate maximum, though duration of that level of activity is somewhat unclear with a total exercise duration including mild stretches of 20-40 minutes at end of program.
Mengshoel 1992	4.5	N = 35 females with FM	Twice-weekly 60 minute exercise dance program for 20 weeks.	At 20 weeks, all patients in the exercise group felt the exercise had "increased their feelings of general well-being." Strength measures increased more in the exercise group, but not statistically significantly.	"Fibromyalgia patients may undergo low-intensity dynamic endurance training without experiencing exacerbation of their general pain and fatigue symptoms."	General pain measured by VAS scores represented as increasing in both groups over duration of study, which does not make sense. Appears to be some errors in data (e.g., dynamic endurance work

RCT				Exercise induced pain decreased in most measures in the exercise group compared with the control group, with some measures decreasing statistically significantly.		measurements). Dropouts higher in exercise group, although indicated to be due to non-fibromyalgia conditions. Exercise targets for study at 120-150 beats per minute may have been low for some patients; they did not appear to target a percentage of estimated maximum heart rate.
McCain 1986 RCT	4.5	N = 34 with FM (Smythe's criteria used)	Cardiovascular fitness training vs. flexibility exercises 3 times weekly for 20 weeks.	Cardio group used bike ergometer and achieved 29.1±24.4% increase in peak work capacity at 170 beats a minute. Total myalgic scores: flexibility (14.7±40.6) vs. cardiovascular fitness (44.4±74.6 kg/m2). Percent changes in total myalgic scores compared with baseline: flexibility 7.0±23.3% vs. cardio fitness 72.9±129.5%. Pain diagram ratings vs. baseline were flexibility 0.8±40 vs. 22.7±114.4%.	"Although these results are preliminary and the statistical analysis is incomplete, the study does show that cardiovascular fitness training improves objective measurements of pain in the fibrositis/fibromyalgia syndrome."	Study claims patient blinding, but this is not tenable.
Jones 2002 RCT	4.5	N = 68 with FM	Twelve week, twice weekly exercise program of muscle strengthening vs. flexibility training.	Total myalgic scores (baseline/follow-up): strengthening (34.2/28.5) vs. flexibility (32.1/27.8). Decreases in numbers of tender points favored strengthening group, as did FIQ pain VAS scores. Twice as many improvements occurred in strengthening than stretching groups.	"Patients with FM can engage in a specially tailored muscle strengthening program and experience an improvement in overall disease activity, without a significant exercise induced flare in pain. Flexibility training alone also results in overall improvements, albeit of a lesser degree."	Dropouts had somewhat higher Beck anxiety scores vs. study completers (22±13.8 vs. 14.3±8.6).
Wigers	4.5	N = 60 with FM	Aerobic exercise (AE) vs. stress	At baseline, TAU group more likely to be out of work (70%)	"Compared to TAU, both AE and SMT induced short-term	Study appears to highlight misconceptions among

1996 RCT			management treatment (SMT) vs. treatment-as-usual (TAU).	vs. 45% of aerobic exercise group and 50% of stress management group. Dropouts involving initiation of additional treatments only occurred in stress management (n = 2) or TAU (n = 3). Results presented graphically and pain distribution (p <0.001), dolorimeter score of tender points (p <0.05), lack of energy (p <0.01), and work capacity (p <0.01) favored aerobic exercise group at end of treatment; results mostly disappeared at follow-up.	fibromyalgia improvement, but no obvious group differences in symptom severity were seen in the longer term." "AE was the overall most effective treatment, despite being subject to the most sceptical patient attitude prior to the study. At follow up, there were no obvious group differences in symptoms severity, which for AE seemed to be due to a considerable compliance problem."	fibromyalgia patients that are against activity, and in favor of passive activity.
Häkkinen 2001 RCT	4.0	N = 21 females with FM (ACR criteria used)	Strength training exercise group vs. no exercise group vs. healthy female control group.	Pain VAS ratings (baseline/post-treatment): exercise group (48/24) vs. controls (35/60). Stanford Health Assessment Questionnaire (HAQ) disability scores: exercise (0.6/0.3) vs. controls (0.7/0.7). Mean height of vertical squat jump lower in fibromyalgia group, but all other strength measures comparable with healthy controls and all measures responded similarly between health controls and FM patients.	"The strength training data indicate comparable trainability of the neuromuscular system of women with FM and healthy women. Progressive strength training can safely be used in the treatment of FM to decrease the impact of the syndrome on the neuromuscular system, perceived symptoms, and functional capacity."	Study suggests benefit of strengthening exercises over flexibility exercises or no exercise.
Gowans 1999 RCT	4.0	N = 41 with FM (ACR criteria used)	Exercise and education program with waiting-list control. Six week treatment of 2 exercise classes and 2 educational sessions per week.	Six-minute walking test distances (baseline/6 weeks): controls (350.6/372.6) vs. intervention (330.7/402.7), p <0.05. FIQ morning fatigue ratings also favored intervention group (p <0.05).	"Short-term exercise and educational programs can produce immediate and sustained benefits for patients with fibromyalgia. The benefits of our program may be due to exercise or education since both interventions were given."	Use of wait listing controls is a recognized bias in favor of intervention group. Baseline non-opioid pain medication use somewhat higher in controls (11/21 vs. 6/20). Co-intervention does not allow

						for separation of effects of each treatment.
Isomeri 1993	4.0	Study reviewed in Anti-depressants Section.				
Jentoft 2001 RCT	4.0	N = 34 with FM (ACR criteria used)	Pool-based aerobic exercise vs. land-based for 20 weeks. Programs consisted of 1 hour of total training per session which included 20 minutes aerobic exercise, 15 minutes strengthening exercise, and education and stretching.	FIQ days of feeling good scores (baseline/ week 20/week 46) were pool (1.8±1.8/3.7±1.7/3.3±2.4) vs. land-based group (2.6±1.7/3.4±2.0/4.1±2.3). Exercise induced pain ratings were pool (23.0±23.3/17.7±21.0/ 13.6±21.7) vs. land-based (22.1±19.8/17.6± 21.6/23.6±23.6). Self-reported physical impairment scores were pool (4.2±1.7/3.4± 1.7/ 3.0±1.9) vs. land-based (3.8±2.0/ 3.1±2.0/ 2.5±1.9).	"Physical capacity can be increased by exercise, even when the exercise is performed in a warm-water pool."	Small study.
Valim 2003 RCT	4.0	N = 76 females with FM	Aerobic exercise program vs. stretching program for 20 weeks. Both programs were 3 times a week for 45 minutes.	Dropouts high in stretching group (26.3%). Dropouts had worse mental health SF-36 scores and higher pain scores. V02Max values rose (baseline/10 weeks/ 20 weeks) in aerobic group (25.4±5.4/27.4± 5.9/28.6±4.7 mL/kg/min) vs. stretching group (24.7±4.4/25.6±6.5/25.2± 4.6). Total FIQ scores: aerobic (5.3±1.5/3.7±2.2/ 3.0±1.9) vs. stretching (4.9±1.6/4.1±1.8/4.0±1.6). Pain scores: aerobic (23.6±8.8/	"Aerobic exercise is beneficial to patients with FM, but the cardio-respiratory fitness gain is not related to improvement of FM symptoms."	Authors' conclusion does not appear to be readily supported by the data. The data support that all major measures either trended or were statistically superior in the aerobic group compared to the stretching group.

				21.3±8.7/ 15.2±9.7) vs. stretching (23.4±8.5/27.6±10.1/ 23.7±10.3).		
Martin 1996 RCT	4.0	N = 60 with FM using ACR criteria	Exercise vs. relaxation.	Tender points decreased in the exercise group (12.79 to 10.22, p <0.05) vs. relaxation (12.94 to 12.89). Fibromyalgia Impact scores also decreased in the exercise program (418.6 to 388.1) vs. relaxation (407.4 to 433.1).	"Exercise is helpful in the management of FM in the short term. It also shows that FM patients can undertake an exercise program which includes aerobic, flexibility, and strength training exercises without adverse effects. The long-term utility of this type of exercise requires further evaluation."	Symptom duration modestly longer in relaxation group (10.4±7.5 vs. 8.9± 6.8 years). Dropouts high in both groups but not given individually (overall dropout rate 36.7%). Mixture of exercises limits ability to infer benefits of individual exercise interventions, though study suggests relaxation therapy is not effective.

Evidence for Yoga

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results	Conclusion:	Comments:
Carson, 2010 (score=7.5)	Fibromyalgia	RCT	Sponsored by a grant from the Oregon Health & Science University Medical Research Foundation and resources supplied by the Fibromyalgia Information Foundation. No COI.	N = 53 participants.	Mean age: 53.7±11.5 years; 0 Males, 53 Females.	Yoga condition (N =25) vs Control condition (N =28)	none	Post-group treatment showed significant improvement favoring yoga in symptoms and functional deficits as well as in pain catastrophizing, and coping strategies. Significant improvement was also observed for yoga group compared to control group for	"(w)omen assigned to the yoga program showed significantly greater improvements on standardized measure of FM symptoms and functioning, including pain, fatigue, mood, pain catastrophizing, acceptance, and other coping strategies."	Pilot study waitlist control bias. Data suggest yoga group improved in pain rating, pain catastrophizing mood, fatigue and acceptance.

								pain (β=-1.47, t=-5.9, p<.0001), fatigue (b = _1.68, t = _6.23, p <.0001), emotional distress (b = _1.34, t = _4.92, p < .0001), and vigor (b = 0.92, t = 3.62, p = .0005); and success at acceptance (b = 1.20, t = 5.10, p < .0001) and relaxation (b = 1.38, t = 4.36, p < .0001) coping strategies.		
Carson, 2012 (score=7.5)	Fibromyalgia	RCT	Sponsored by a grant from the Oregon Health & Science University Medical Research Foundation and resources supplied by the Fibromyalgia Information Foundation. No COI.	N=39	Mean age: 55.4±11.3 years. 0 males, 39 females.	Immediate treatment (n=21) vs waitlist (n=18)	3 months	Significant associations were observed with greater daily relaxation (t=3.49, p=.001). More yoga poses also showed to improve pain (t= _2.31, P=0.027), lower daily fatigue (t= _2.02, P=0.052), lower daily distress (t= _2.07, P=0.047), higher daily vigor (t=2.68, P=0.011), lower FIQR fatigue scores (t= _1.86, P=0.072), lower	"These findings indicate that the benefits of Yoga in fibromyalgia are replicable and can be maintained."	Waitlist control bias. Data suggest yoga may show benefits for FM patients.

								FIQR Impact subscale scores (t= _2.09, P=0.045), and lower pain catastrophizing (t= _1.86, P=0.072).		

Evidence for Swimming

Fernandes 2016 (6.5)	Aquatic Therapy	RCT	Supported by the Sao Paulo Research Foundation (grant no. 2010/51238-9). Clinical Trial Registration No.: NCT01547195. No COI.	N = 75	Mean age is 48.8 years. 0 males, 75 females.	Walking group (N = 36) vs. Swimming group (N = 39)	Evaluated at t=0, 6, and 12 weeks.	There were no significantly significant differences with analyses between groups at each evaluation time. Pain between groups were low (.168; 95% CI, .59-.92) P = .658.	"A swimming and walking program had similar and beneficial effects on pain, functional capacity, and quality of life in patients."	Data suggest comparable efficacy where either swimming 50 min/d times 3 days/wk for 12 weeks is as beneficial as walking 50 min/d times 3 days/wk for 12 weeks.

Evidence for Aquatic Therapy Other than Swimming

Manerkorpi 2009 (5.5)	Aquatic Therapy	RCT	Supported by grants from the Swedish Rheumatism Association, the Vardal Foundation, and the Lansforsakringsbolagen Research Foundation. No mention of COI.	N = 58	Mean age is 56 years old.	Control Group (N = 30) vs. Treatment Group (N = 28)	Once a week for 6 months	FIQ physical functioning (p = 0.001) and anxiety (p = 0.019) were improved in the training group compared to the control group. The FIQ scores for FIQ total (p = 0.003), physical functioning (p = 0.004), pain (p = 0.01), fatigue (p = 0.004), stiffness (p = 0.002), and anxiety (p =	"The results suggest that a 6 month program of exercises in a temperate pool combined with education will improve the consequences of FM."	Significant dropout. Data suggest small improvement in combination therapy.

								0.006) all improved.		
Assis 2006 (5.0)	Aquatic Therapy	RCT	Supported by a grant from FAPESP (Research Support Fund of the State of Sao Paulo). No mention of COI.	N = 60	60 females, 0 males. Mean age is 42.8 years.	LBE group (N = 30) vs DWR group (N = 30).	3 months	FIQ scores were improved in both groups. The LBE group and DWR group ($p < 0.001$). Greater improves were achieved by the DWR group at week 15 ($p = 0.033$, 95% CI 0.764-21.955).	"Aerobic exercise in a warmed swimming pool was as effective as a land-based program in treating patients with FM regarding pain."	Data suggest comparable efficacy (i.e. deep water running).
Cedraschi, 2003 (5.0)	Self-management	RCT	Supported by Swiss National Foundation for Research, No mention of COI.	N = 164 patients with fibromyalgia.	Mean age: Treatment group 48.9, Control group 49.8. Sex(M:F) 12:152	Treatment group (N=84) (TG) received a 12-session programme meeting 2x/wk for 6 weeks. The programme included the promotion of self-management and exercise sessions. The waitlist group (WL) (N=80) was offered the programme after the 6 month follow up.	6 months	The treatment group in comparison to the WL group (Mean difference from baseline to follow up TG vs WL) had significant improvement in PGWB (anxiety) (-1.6 vs 0.5 (p=0.011)), vitality (-0.9 vs 0.2 (p=0.013)), and total scores (-5.2 vs 0.2 (p=0.007)). TG in comparison to WL also had significant improvements in total FIQ score (0.6 vs 0.1 (p=0.02)), pain (0.2 vs -0.6 (p=0.02)), fatigue (1.0 vs -0.3 (p=0.003)), and depression (0.9 vs -0.2 (p=0.03)).	"A 6 week self-management based programme of pool exercises and education can improve the quality of life of patients with FM and their satisfaction with treatment."	Waitlist control bias. Data suggest a 6 week self-managed program of pool exercise and education can improve quality of life and treatment satisfaction in fibromyalgia patients.

Munguia-Izquierdo 2008 (4.5)	Aquatic Therapy	RCT	Supported by the European Social Funds and Regional Government of Aragon (Spain: grant B187/2004).	N = 60	60 females, 0 males. Mean age is 47.5 years.	Exercise group (N = 29) vs. Control group (N = 24) vs. Healthy group (N = 25). (For efficacy analysis).	Treatment of 16 weeks.	Efficacy and ITT analysis showed similar baseline characteristics for the exercise, control, and healthy groups. The healthy group showed significantly better efficacy and ITT analyses results. Exercise group showed a statistically significant improvement in the FIQ (p = 0.020) for efficacy and (P = 0.005) for ITT.	"Exercise therapy program with moderate intensity performed 3 times a week for 16 weeks in a chest-high pool of warm water has no apparent negative effects and improves pain, sleep quality, and physical and cognitive function."	Non-interventional control, thus susceptible to biases. Data suggest benefit from 3x/wk exercise in warm pool for FM symptoms.
de Melo Vitorino 2005 (4.0)	Aquatic Therapy	RCT	No mention of sponsorship or COI.	N = 50	50 females, 0 males. Mean age is 47.7 years.	Hydrotherapy (N = 24) vs. Conventional physiotherapy (N = 26).	Three weeks	The mean TST of both groups increased in relation to the pretreatment period (P<0.0001). The HT had a higher number of patients with improved TST (P<0.01). All HT patients increase at least 1 h in TST compared to 19 CP patients (P = 0.04). TNT decreased in both groups but mostly	"In conclusion, HT and CP are equally effective to improve QOL for FM patients, but HT is more effective than CP to improve TST and to decrease TNT."	Small sample data suggest hydrotherapy is better than standard physiotherapy for decreasing total nap time and improving total sleep time.

								in the HT group (P<0.05).		
Gusi 2006 (4.0)	Aquatic Therapy	RCT	Supported by the European Social Funds and Regional Government of Extemadura (Spain; grant 2PR02B017 and Health Department).	N = 34	34 females, 0 males. Mean age is 51 years.	Exercise (N = 17) vs. Control (N = 17)	12 weeks, 24 weeks, 12 weeks.	The strength of the knee extensors in concentric actions increased by 20% in both limbs after the training period, and these improvements were maintained after the de-training period in the exercise group. The strength of other muscle actions measured did not change. HRQOL improved by 93% (P = 0.007) and pain was reduced by 29% (P = 0.012) in the exercise group.	"The therapy relieved pain and improved HRQOL and muscle strength in the lower limbs at low velocity in patients with initial low muscle strength and high number of tender points. Most of these improvements were maintained long term."	Data suggest the exercise group (resistance, aerobic and strengthening in pool) reported less pain and improved QoL measures.
Tomas-Carus 2009 (4.0)	Aquatic Therapy	RCT	The study was supported by the European Social Funds and the Government of Extremadura, Spain (2PR02B017 and Health Department). No COI.	N = 30	30 females, 0 males. Mean age is 50.8 years.	Experimental Group (N = 15) vs. Exercise Group (N = 15)	3 weekly sessions	Concentric knee flexors strength predicted improvements in the role of physical problems P = 0.002. Gains in concentric knee extensors strength predicted improvements in the role of emotional	"A long-lasting exercise therapy in warm water produced relevant gains in muscle strength at low velocities of movements, some of which predicted improvements in physical problems, emotional problems, mental	Data suggest significant benefit in muscle strength and balance as well as improved emotional and psychological improvement from 32 weeks of aquatic training.

								problems P = 0.002.	health and balance."	
Munguia-Izquierdo 2007 (4.0)	Aquatic Therapy	RCT	Supported by the European Social Funds and Regional Government of Aragon (Spain: grant B187/2004).	N = 78	Mean age is 47.8 years. 0 males, 58 females.	Exercise (N = 29) vs Control (N = 24) Vs. Healthy (N =25).	Follow-up at 16 weeks	The exercise group presented an incremental significance in higher pain threshold.	"An exercise therapy three times per week for 16 weeks in a warm-water pool is an adequate treatment to decrease the pain and severity of FM well as to improve cognitive function in previously unfit women with FM and heightened painful symptomatology."	Data suggest warm pool exercise (3x1up) for 16 weeks helps to significantly reduce FM pain severity.

Evidence for Tai Chi

Calandre, E 2009 (Score = 4)	Fibromyalgia	RCT	No mention of sponsorship or COI.	N = 81 with FM and sleep quality.	8 males, 73 females; Mean age 49.9	Tai Chi vs Stretching	3 months	FIQ scores total endpoint; stretching .038, Tai Chi 0.15.	"Although no global difference were found between groups, Tai Chi significantly improved fibromyalgia symptomatology and sleep quality, whereas stretching only improved subjects' psychological well-being."	Significant dropout at final follow up. Data suggest Tai Chi improved sleep quality in FM patients but stretching has positive benefit on psychological well-being.
Jones, k 2012 (Score = 4)	Fibromyalgia	RCT	Sponsorship from funding by; National Institutes of	N = 98 with FM	91 females, 7 males; mean age 54.	Tai chi 90 mins twice weekly	12 weeks	FIQ scores (16.5 vs. 3.1, (p = 00.0002), BPI pain	"Tai chi appears to be a safe and an acceptable	Data suggest tai chi may be a good adjunct therapy in

			Heal/NIAMS. No mention of COI.			vs control.		severity (1.2 vs. 0.4, (p = 00.0008), BPI pain interference (2.1 vs. 0.6, (p = 00.0000), sleep (2.0 vs. −0.03, (p = 00.0003), and self-efficacy for pain control (9.2 vs. −1.5, (p = 00.0001). Functional mobility variables including timed get up and go (−.9 vs. −.3, (p = 00.0001), static balance (7.5 vs. −0.3, (p = 0 0.0001), and dynamic balance (1.6 vs. 0.3, (p= 00.0001)	exercise modality that may be useful as adjunctive therapy in the management of FM patients."	managing FM patients.
Wang, C 2010 (Score = 5)	Fibromyalgia	RCT	Sponsorship by a grant from the National Center for Complementary and Alternative Medicine of the National Institutes of Health, the American College of Rheumatology Research and Education Foundation Health Professional Investigator Award, and the Boston Claude D. Pepper Older Americans independence Center Research Career	N = 66 who fulfilled the 1990 American College of Rheumatology fibromyalgia criteria	57 female, 9 male. Mean age tai chi group 49.7±11.8 years, control group 50.5±10.5 years	Tai Chi 2 times weekly for 60 mins (N = 33) vs Control wellness education and stretching (N = 33)	12 and 24 weeks	FIQ scores for the tai chi group were 62.9±15.5 and 35.1±18.8 vs 68.0±11 and 58.6±17.6. Change from baseline in the tai chi group vs control −18.4 points; (P < 0.001). Difference in the FIQ score, −18.3 points; (p < 0.001) SF-36 physical-component	"Tai chi may be a useful treatment for fibromyalgia and merits long-term study in larger study populations."	Data suggest Tai Chi maybe beneficial for treatment of FM patients as Demonstrated in FIQ scores.

			Development Award. No mention of COI.					scores were 28.5±8.4 and 37.0±10.5 for the tai chi group versus 28.0±7.8 and 29.4±7.4 for the control group (between-group difference, 7.1 points; (p = 0.001), and the mental component scores were 42.6±12.2 and 50.3±10.2 for the tai chi group versus 37.8±10.5 and 39.4±11.9 for the control group (between-group difference, 6.1 points; (p = 0.03)		

Evidence for Spa and Balneotherapy

Altan L, 2004 4.5	Balneotherapy	RCT	No sponsorship or COI.	N = 50 patients with fibromyalgia.	The mean age of group 1 is 43.14 years. 0 males, 24 females. The mean age of group 2 is 43.91 years. 0	Group 1 (N = 24) – patients received a pool-based exercise program by a physiotherapist in a therapeutic pool for 35 mins a day, 3 times a week. Program included warming,	Evaluation were performed at week 0, 12, and 24.	At week 12 and week 24, group 1 and group 2 reported the following results, respectively, based on the visual analogue scale, and fibromyalgia impact questionnaire. Pain (VAS): week	"In conclusion, the results of our study did not a show a significant superiority of pool-based exercise over balneotherapy without exercise. However, since the	Data suggest comparable efficacy between exercise and no-exercise groups, but pool based therapy had sustained benefits for some symptoms at 6 months.

					males, 22 females.	activity, relaxation, and out of the pool exercises. vs group 2 (N = 22) - patients received balneotherapy sessions of 35 min three times a week for 12 weeks in the same pool, but they were instructed not to perform any exercise during the sessions.		12 (-0.24±0.28, -0.23±0.22), week 24 (-0.30±0.34, -0.13±0.31). Pain (5-point scale): week 12 (-0.27±0.35, -0.28±0.23) week 12 -0.35±0.31, -0.18±0.37). Fatigue (VAS): week 12 (-0.33±0.39, -0.15±0.19) week 24 (-0.16±0.79, -0.11±0.28). Fatigue (5-point scale): week 12 (-0.37±0.38, -0.19±0.23) week 24 (-0.29±0.38, -0.24±0.32). Number of tender points: week 12 (-0.43±0.27, -0.36±0.2) week 24 (-0.41±0.26, -0.33±0.29). FIQ: week 12 (-0.21±0.32, -0.11±0.19) week 24 (-0.18±0.36, -0.07±0.27). Chair test: (-0.01±0.14, -0.09±0.21) week 24 (-0.009±0.13, -0.03±0.13). Beck depression inventory: week 12 (-0.33±0.38, -0, 01±0.33, P<0.01) week 24 (-	evaluation results at the end of 6 months showed that improvements in the parameters of sleep and morning stiffness were maintained in the exercise group vs the control group, we suggest that pool-based exercise has a longer-lasting effect on at least some of the symptoms of FMS."	

								0.3±0.38, -0.008±0.47, P<0.05).		
T. R. Zijlstra, 2005 4.0	Thalassotherapy	Diagnostic	Sponsored by the Dutch Arthritis Association, grant NR 97-1-303. No mention of COI.	N = 134. 58 patients with fibromyalgia subjected to the spa treatment and 76 patients with fibromyalgia not subjected to the spa treatment.	The mean age of the spa treatment group is 48 years. 3 males, 55 females. The mean age of the control group is 47 years. 3 males, 73 females.	Spa Treatment (N = 58) – received 2 ½ weeks of treatment in a Tunisian spa resort, including thalassotherapy, supervised exercise, and group education vs Control (N = 76) – patients were told they are participating in an observational study to assess the impact of fibromyalgia on several aspects of health and social functioning.	Patients were evaluated at baseline, 1 month, 3 months, 6 months, and 12 months.	The primary outcome measure was measured with the RAND-36 questionnaire. The physical component results between the spa and control, respectively, are the following: Baseline: 28.6, 27.8. 1 month: 6.3 (p<0.001), - . 3 months: 3.6 (p=0.02), 0.8. 6 months: 1.3, 0.5. 12 months: 2.6, 1.6. The mental component results between the spa and control groups, respectively, are the following: baseline: 45.7, 46.5. 1 month: 6.5 (p<0.001), - . 3 months: 0.8, 1.2. 6 months: 0.2, 0.1. 12 months: -2.2, 0.5.	"In conclusion, a combination of thalassotherapy, exercise and patient education can produce significant subjective improvement in patients with FM, lasting for 3–6 months."	Usual care bias. Intervention for patients in Tunisian spa.

Evidence for Fear Avoidance Belief Training

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Palstam, 2016 (6.5)	Fear Avoidance	Sub-study of RCT	Supported by Swedish Rheumatism Association. No COI.	N = 67 patients with Fibromyalgia.	Mean age: 51 Sex(M:F) 0:67	Participants completed a 15 week intervention consisting of performing progressive resistance exercise twice a week.	15 weeks.	Improvement in pain disability was explained 28% (p=0.005) by high pain disability at baseline, and improvement in fear avoidance beliefs. High baseline scores and improvement in fear avoidance explained the Improvement in recreation and social activity by 32% (p=0.0025) and 30% (p=0.017) respectively.	"The reduced pain disability seemed to be mediated by decreased fear avoidance beliefs."	Sub study of original RCT (secondary analysis). Data suggest a decrease of fear avoidance beliefs after person-centered progressive resistance exercise is associated with a reduction in pain disability in fibromyalgia women.

Evidence for Whole Body Vibration

Olivares, P 2011 (Score = 6)	Fibromyalgia	RCT	No mention of sponsorship, no COI.	N = 36 patients with FM	36 females; mean age 52.7.	Tilting WBV (12.5-Hz frequency; 3-mm amplitude 12 weeks. (N = 18) vs Control (N = 18)	12 weeks	Efficacy after 12 weeks training exercise vs control. 56.72 vs 57.49 (p = 0.033). Intent to treat exercise vs control. 55.40 vs 59.13 (p = 0.046).	"Tilting WBV was a feasible intervention that prevented the loss of HRQoL in previously physically untrained women with FM."	Data suggest WBV may be used to maintain QOL as measure in an improved FIQ score but difference minimal.
Gusi, N 2010 (Score = 5.0)	Fibromyalgia	RCT	No mention of Sponsorship or COI.	N = 36 patients with FM.	36 females; Mean age	Vibration group 12 weeks, 12.5 Hz frequency and 3 mm amplitude (N = 21) vs Control (N = 20)	12 weeks	Dynamic balance of Vibration group improved by 36%, control unchanged. Change after 12 weeks exercise -.64 vs control .44 (p = < 0.001).	"The vibration program was useful and feasible for improving dynamic balance in women with FM. These novel results support further research aimed at the	Data suggest hit WBV was useful in improving dynamic balance in women with FM.

									development of physical therapy programs that utilize controlled vibration."	
Adsuar, J 2012 (Score = 5)	Fibromyalgia	RCT	No sponsorship or COI.	N = 36 patients with FM.	36 females; Mean age	Vibration group 12 weeks, 12.5 Hz frequency and 3 mm amplitude (N = 21) vs Control (N = 20)	12 weeks	OSI exercise vs control. 0.88 vs 1.40 (p = 0.003) APSI exercise vs control 0.56 vs 0.96 (p < 0.001) MLSI exercise vs control. 0.55 vs 0.83 (p = 0.231)	"Tilting whole-body vibration therapy effectively improves static balance in patients with FM."	Data suggest tilting WBV improves static balance in FM patients.
Sañundo, B 2013 (Score = 4.5)	Fibromyalgia	RCT	Sponsorship by funds from the Andalusian Center of Sport Medicine and the University of Seville. No mention of COI.	N = 46 patients with FM	46 females mean age 58.4	Exercise training and whole body vibration (WBV). performed twice-weekly exercise sessions (aerobic exercise, strengthening and flexibility) combined with 3 whole-body vibration training sessions a week (bilateral squats: 6–9 sets of 30 s with 45-s recovery between sets; and unilateral squat: 4–7 sets of 30 s, 30 Hz–4 mm) (N = 15) vs	8 weeks	Improvement WBVEX over the EX group (p = 0.014) and over the CG (p = 0.029)	"The results show that a traditional exercise programme, supplemented with whole-body vibration training improved balance in women with fibromyalgia. This may represent a key factor for falls prevention in this patient group."	Many baseline differences.

						Exercise group (N = 15) vs Usual care control group (N = 16).				
Alentorn-Geli, E 2008 (Score = 4.5)	Fibromyalgia	RCT	No sponsorship or COI.	N = 36 patients with FM	36 females; mean age 55.97	Exercise and Vibration. 15 minutes of a warmup, 30 minutes of aerobic exercise, 25 minutes of stretching exercises, and 20 minutes of relaxation. 30 Hz of frequency and 2 mm of amplitude Major Thirty (30) Hz has been shown to induce maximal muscular electrical activity.(N = 12) vs Exercise (N = 12) vs control group (N = 12)	6 weeks	3 X 2 (group X time)-repeated measures analysis of variance interaction was found for pain (p = 0.018) and fatigue (p = 0.002) but not for FIQ (p = 0.069), stiffness (p = 0.142), or depression (p = 0.654).	"Results suggest that a 6-week traditional exercise program with supplementary WBV safely reduces pain and fatigue, whereas exercise alone fails to induce improvements."	Data suggests that after 6 weeks a combination exercise program plus WBV reduces pain than a combination exercise program alone.
Alentorn-Geli, E 2009 (Score = 4)	Fibromyalgia	RCT	No sponsorship or COI.	N = 24 patients with FM	24 females; Mean age 54.95	Vibration Group WBV intensity was kept constant at 30 Hz frequency and 2mmamplitude	6 weeks	There was an absence of change in IGF-1 at week 1 and week 6 of whole-body vibration exercise.	"Results show no change in serum IGF-1 levels in women with fibromyalgia undergoing whole-body vibration exercise.	Small sample data suggest each of efficacy.

						(low amplitude) six exercises (30 seconds each) were repeated six times with a recovery time of 3 minutes in between (N = 12) vs Control group (N = 12)			Although high-intensity exercise and whole-body vibration exercise have been shown to increase serum IGF-1 in healthy individuals, the effectiveness of whole-body vibration exercise as a strategy to produce improvements in serum IGF-1 levels in women with fibromyalgia could not be demonstrated."	

Devices

Evidence for Kinesiotaping/Taping

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Vayay 2016 Score: 4.5	Chronic, Fibromyalgia	RCT	No mention of COI or sponsorship.	N = 38 participants diagnosed with fibromyalgia	Mean age 37.47. 0 male, 45 females.	Laser (3 min per 17 painful points, 2J/cm^2 40mw, 850 nm wavelength) group, received laser and exercise program (N = 15), vs placebo laser group, received sham laser and exercise program (N = 15), vs taping group, received kinesiotaping and exercise program (N = 15). All groups received 5 treatments per week for 3 weeks.	Follow-up at 15 days and 3 weeks.	Significant results seen in decrease of pain at night for laser, placebo laser, and taping groups (p=0.04, p=0.001, p=0.001 respectively). Significant pain reduction during exercise was found in laser group only (p=0.02). Significant improvement in FIQ for laser, placebo laser, and taping groups (p<0.001, p<0.001, p=0.01 respectively). Significant body flexion flexibility increase in placebo laser and taping groups (p<0.001, p-0.03), and significant increase in hyperextension flexibility in taping group (p=0.02). Significant improvement in Beck Depression Scale for laser (p=0.01) and taping group (p=0.01).	In this study where the impact of the Laser application and taping on pain, function and quality of life of the cases diagnosed with fibromyalgia all treatment groups were found to be effective on different parameters. While it is observed that the three-week Laser and taping in FMS improved the general health level, depression and anxiety and increase functionality similarly, the Laser application additionally led to decrease in pain level and increase in body flexion flexibility and the taping led to increase in body hyperextension flexibility."	Data suggest comparable benefits for FM between kinesiotaping and laser but the laser groups reported less pain.

Evidence for Magnets/Magnetic Stimulation

Alfano, A 2001 (Score = 4.5)	Fibromyalgia	RCT	Supported in part by a grand from the National center for Compleme ntary and Alternative Medicine, National Institutes of Health, and a gift from a large privet Canadian charitable foundation.	N = 111 with Fibromy algia	103 females, 8 males; mean age 45.4	Pad A used pad for 6 months provided whole body exposure to a low, uniform magnetic field. (N =37) vs Pad B used a pad for 6 months that exposed them to low static magnetic field that varied spatially and in polarity (N =30) vs Sham Pads (A-B) (N = 27) vs Usual care (N = 17)	6 months	The overall comparison of FIQ change scores at 6 months among the four groups was not statistically significant (F = 3.88, (3, 88) *df*, (*p* = 0.23). Overall test comparing groups was statistically significant (F 5 3.07, 3, 88) *df*, (*p* =0.031) Average change scores between groups (F = 0.46, (3, 86) *df*, (*p* = 0.72)	"Although the functional pad groups showed improvements in functional status, pain intensity level, tender point count, and tender point intensity after 6 months of treatment, with the exception of pain intensity level these improvements did not differ significantly from changes in the Sham group or in the Usual Care group."	Sparse methods, data suggests a significant pain intensity improvement with functional pad A but all other groups showed similar improvement at 6 months.

Medications

Evidence for Oral NSAIDs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Quijada-Carrera 1996 (4.5)	Tenoxicam and Bromazepan	RCT	No mention of sponsorship or COI.	N = 164	Mean age is 43 years; 153 females, 11 males.	Tenoxicam + Bromazepan (N =35) vs. Tenoxicam (N =24) vs. Bromazepan (N =25) vs. Placebo (N = 26)	8 week assessment	There seemed to be no significant difference between any of the 4 treatment groups at 3 weeks of treatment. 12 patients of 164 with tenoxicam+bromazepan showed significant improvement compared to 7, 4, and 5 patients in the placebo, tenoxicam, and bromazepan groups. P = 0.049 between tenoxicam+ bromazepan and tenoxicam.	"Tenoxicam and bromazepan showed efficacy in a small percentage of patients with fibromyalgia; however, this combined therapy was not significantly better than placebo."	Data suggest a trend towards improvement with tenoxicam plus bromazepan but these were not significant.
Goldenberg 1986 (5.0)		RCT		N = 62 with FM (Yunus case criteria used)		Amitriptyline 25mg QHS vs. naproxen 500mg BID vs. both medications vs. placebo		Tender point scores decreased in the amitriptyline group (14.5 to 11.6) vs. the combination medication group (13.8 to 8.2). Pain ratings decreased in the amitriptyline group (7.3 to 5.4) vs. the combination medication group (6.9 to 4.7).	"Our trial demonstrated that amitriptyline and naproxen given over a 6-week period, is an effective treatment for patients with fibromyalgia, and should be considered in patients with symptoms of this common condition."	Suggests amitriptyline superior to naproxen and combination of medications results in "minor" additional reductions in pain. Baseline scores somewhat higher in amitriptyline group, suggesting

										effects of amitriptyline vs. other treatments somewhat underestimated. Despite other 2 treatment arms, data only for amitriptyline and combined medication.

Evidence for Acetaminophen

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Meeus M 2013 (6.5)	Fibromyalgia	RCT	There was no external funding in the preparation of this manuscript. No Conflict of interest:	N= 53 women (19 Chronic Fatigue Syndrome /Fibromyalgia patients, 16 Rheumatoid arthritis patients, and 18 healthy women)	Mean age: 46.6 years; all women.	Experimental group (1 g acetaminophen) vs. the placebo group (1 g dextrose)	Not mentioned	After intake of acetaminophen, pain thresholds increased slightly in CFS/FM patients, and decreased in the RA and the control group. Temporal summation was reduced in the 3 groups and CPM at the shoulder was better overall, however only statistically significant for the RA group. Healthy controls showed improved CPM for both finger and	This cross-over RCT showed that acetaminophen may partly support conditioned pain, but that other contributors than serotonergic pathways should be identified."	Crossover design. Population composed of RA, CFS and FM patients. Data suggest acetaminophen may have only a limited positive benefit on the central pain inhibition of CFS/ FM patients.

								shoulder after acetaminophen, although not significant		
Bennett, R.M. 2003 (5.5)	Tramadol and Acetaminophen	RCT	Sponsored by a grant (CAPSS-113) from Ortho-McNeil Pharmaceutical, Inc, Raritan, New Jersey. All investigators were financially reimbursed by Ortho-McNeil Pharmaceutical for conducting this study. No mention of COI.	N = 315 patients with fibromyalgia.	The mean age of the Tramadol/Acetaminophen Group is 49 years. 11 males, 145 females. The mean age of the placebo group is 51 years. 8 males, 149 females.	Tramadol/Acetaminophen (n=156) – patients received combination tablets (37.5mg/325mg tablets) Vs. Placebo (n=157) – patients received the matching placebo	No follow-up.	The primary efficacy outcome is the cumulative rate of discontinuation of therapy. It was significantly lower in the Tramadol/Acetaminophen group than the Placebo group. The number of patients continuing the tramadol/APAP treatment was 73 and number or patients continuing the placebo was 51 at day 91. P=0.004.	"A tramadol/acetaminophen combination tablet was effective for the treatment of fibromyalgia pain without any serious adverse effects."	Data suggests combination of tramadol/acetaminophen reported less pain at conclusion of study.
Meeus M, 2015 (5.0)	Exercise	RCT	Sponsored by funded by ME Research UK. No COI.	N = 53 patients with either rheumatoid arthritis, chronic fatigue syndrome and fibromyalgia, or controls.	The mean age for the RA patients is 54.25 years. The mean age for the control group is 41.06 years. The mean age of the CFS/FM group is 44.58 years. 0 males, 53 females.	Paracetamol – Patients were given 1g paracetamol before exercise. Vs. Placebo – Patients were given 1g dextrose before exercise. (n=) was not specified by author.	No follow up.	The verbal numeric rating scale scores for patients with fibromyalgia in the finger was 5.16 before exercise and 5.00 after exercise. The VNRS in the shoulder was 4.64 before exercise and 5.11 after exercise.	"This study evaluates pain scores, TS, and CPM in response to submaximal exercise in 2 different chronic pain populations and healthy controls. In patients with RA, exercise had positive effects on	Crossover design. Single dose study only.

									TS, suggesting normal EIA. In patients with CFS/FM, these positive effects were only observed after paracetamol and results were inconsistent."	

Evidence for Anti-depressants

Arnold 2002 RCT	8.0	N = 60 females with FM (ACR criteria used), 57% fluoxetine and 67% in placebo history of depression	Titrated doses of fluoxetine (10-80mg a day, mean dose 45±25mg a day) with placebo for 12 weeks.	Fibromyalgia Impact Questionnaire (FIQ) scores were -8.6±14.5 in fluoxetine vs. 2.9±13.6 among placebo (p = 0.005). McGill Pain Questionnaire scores had a similar pattern (-10.8±12.3 vs. -1.8±11.9, p = 0.01).	"Fluoxetine was found to be effective on most outcome measures and generally well tolerated in women with fibromyalgia."	Dropout rates high in both groups (36.7% vs. 40.0%).
Volkmann 1997 Randomized Crossover Trial	8.0	N = 34 with FM	Intravenous S-adenosyl-L-Methionine (SAMe) vs. placebo. Treatment periods daily for 6 days, then 1 day off and another 4 days of treatments.	Pain at rest decreased from 65/100 to 56 for SAMe while change was 65 to 69 on placebo (p = 0.08).	"Study only showed statistically non-significant trends towards a beneficial effect of i.v. SAMe in FM with regard to certain subjective symptoms. However, due to lack of statistical power and since the present findings were in line with previous results, we cannot discard the possibility of a moderate beneficial effect of SAMe in FM."	Four patients dropped out due to adverse effects of SAMe.
Arnold 2004 RCT	7.5	N = 207 with FM, 88.9% females, 38.2% had current major depressive episode	Duloxetine vs. placebo for 12 weeks. Duloxetine increased at 20mg/day increasing to 60mg/day.	Differences in improvements in fibromyalgia impact scores: -4.52, p = 0.042. Females responded more than males in FIQ scores (p = 0.029).	"Duloxetine was an effective and safe treatment for many of the symptoms associated with fibromyalgia in subjects with or without major depressive disorder, particularly for women, who had	Other psychiatric disorders unclear and depressive symptoms not described. Dropouts high in acute phase, higher in duloxetine (44%) than placebo (36%). More

					significant improvement across most outcome measures."	prior anti-depressant use in placebo group.
Caruso 1987 RCT	7.5	N = 60 with primary fibromyalgia syndrome (PFS)	Dothiepin 75mg QHS vs. placebo.	Percentage changes in tender points significant in dothiepin group (-51.5% vs. -15.8%, p <0.01). Results for subjective pain severity also significant for dothiepin (-38.4% vs. -8.7%, p <0.01).	"Therapy with dothiepin seems to be useful in reducing pain in patients with PFS and shows a good tolerability with only mild and transient side effects."	Authors note that further studies needed to confirm these data and "eventually to establish the appropriate dosage and length of treatment for this type of 'extra-articular rheumatism'."
Arnold 2005 RCT	7.5	N = 354 females with FM	Duloxetine 60mg QD vs. 60mg BID vs. placebo for 12 weeks	Response rates were 33% placebo vs. 55% daily dose vs. 54% twice daily dose groups.	"Both duloxetine 60mg QD and duloxetine 60mg BID were effective and safe in the treatment of fibromyalgia in female patients with or without major depressive disorder."	Dropout rates elevated in placebo (43%) and duloxetine (35% and 39%). Data suggest no significant differences in efficacy between active treatment arms. Adverse effects somewhat higher in duloxetine.
Späth 2004 RCT	7.5	N = 21 females with FM	Five daily intravenous bolus injections of 5mg tropisetron vs. placebo injections.	Graphic data indicate pain scores significantly lower in tropisetron group (p = 0.038) while VAS pain scores nearly significant (70 to 41.1 vs. from 64.4 to 57.7, p = 0.063). Baseline data suggest time since diagnosed favored placebo (2.9±5.3 vs. 0.4±0.7 years, labeled not significant).	"5-HT receptor antagonists provide significant pain relief for a group of FM patients."	Medication administration invasive, requiring daily treatments.
Goldenberg 1996 Double-blind Crossover Trial	7.0	N = 19 with FM (ACR criteria used)	Fluoxetine 20mg QD (FL) vs. amitriptyline 25mg QD (AM) vs. 2 medications combined vs. placebo. Two-week washout phase	Mean symptoms duration shorter among dropouts (7.26±48.1 vs. 57.0±26.1 months, p = 0.15). FIQ scores at 6 weeks: placebo 58.5±17.1 vs. amitriptyline 52.3±22.9 vs. fluoxetine 47.6±19.8 vs. combination 38.0±21.2 (p <0.03). VAS pain ratings at 6	"Both FL and AM are effective treatments for FM, and they work better in combination than either medication alone."	More dropouts on fluoxetine citing increased symptoms (3 vs. 1 in washout phase). Overall dropout rate high (38.7%).

			between 4 6-week trials.	weeks: 81.5±16.5 vs. 64.4±28.3 vs. 57.5±25.7 vs. 42.9±28.5, p <0.02.		
Fors 2002 RCT (with two randomization processes	7.0	N = 55 females with FM (ACR criteria used)	Amitriptyline 50mg a day (increased 10mg each day until 50mg reached Day 11) vs. placebo and comparing relaxation training and guided instruction in "pleasant imagery" vs. relaxation training and attention imagery upon "active workings of internal pain control systems" vs. control group.	Peasant imagery significantly improved symptoms (p <0.005), but not other 2 arms. Data are presented graphically and indicate that pleasant imagery group had lowest pain ratings, while control group was intermediate and attention imagery group had worst ratings.	"Pleasant imagery (PI) was an effective intervention in reducing fibromyalgic pain during the 28-day study period. Amitriptyline had no significant advantage over placebo during the study period."	All 3 treatment arms included selecting an unlabeled relaxation tape, but control tape was blank, which provided a probable bias against that group, although they did get a 30-minute walk by a family physician in lab.
Carette 1986 RCT	6.5	N = 70 with primary fibrositis (Smythe's criteria used)	Amitriptyline 50mg vs. placebo control for 8 weeks. Amitriptyline gradually increased (10mg QHS for 1 week, 25mg QHS for 2 weeks and 50mg QHS for 5 weeks).	Morning stiffness scores (baseline/5 weeks/9 weeks): amitriptyline (75±72/41±58/48±61) vs. placebo (78±71/71±80/ 66±76; p <0.05 for amitriptyline group compared with baseline). Pain analog scores showed similar result: amitriptyline (6.3±3.2/ 3.8±2.3/4.3±3.0) vs. placebo (5.8±2.4/5.3± 2.7/5.0±3.0) (p <0.05 for amitriptyline compared with baseline). Most in amitriptyline experienced improvements (77% at 5 weeks vs. 43% placebo; p = 0.008) while at 9	"Our data indicate that amitriptyline is effective in relieving symptoms of fibrositis but has little effect on fibrositic point tenderness."	Baseline differences of longer symptom duration among placebo group (mean 71±58 vs. 97±87 months for placebo, p = 0.04) may have favored amitriptyline, although pain ratings somewhat higher in amitriptyline group (6.3±2.3 vs. 5.8±2.4). Sample sizes appear to have resulted in underpowered study.

				weeks, results not significant (70% vs. 50%, p = 0.11).		
Tavoni 1987 Crossover Trial	5.5	N = 17 with FM	Intramuscular injections of SAMe 200mg vs. placebo injections.	Number of trigger points plus painful anatomic sites decreased after administration of SAMe (p <0.02) but not after placebo treatment. Scores on Hamilton Depression Rating Scale and SAD rating scales improved after SAMe administration (p <0.05 and p <0.005, respectively), did not significantly change after placebo treatment.	"This preliminary study confirms that close relationship between primary fibromyalgia and psychologic disturbances, particularly with regards to a depressive state. SAMe treatment, by improving the depressive state and reducing the number of trigger points, seems to be an effective and safe therapy in the management of primary fibromyalgia."	Results not well reported, but graphically appear to indicate no significant differences between two groups. Study details not well defined.
Goldenberg 1986	5.0	Study reviewed in NSAIDs section.				
Hannonen 1998	5.0	N = 74 females with FM	Moclobemide (MOCLO) 150mg BID plus placebo amitriptyline QHS vs. moclobemide placebo plus amitriptyline	Pain ratings (baseline/end): moclobemide (5.7±2.1/4.5±2.7) vs. amitriptyline (5.8±1.8/4.4±2.6) vs. placebo (5.9±2.0/5.3±2.5). Dropout rates high in all arms (mean 29.2%).	"MOCLO may not be helpful in (fibromyalgia) patients free from clinically meaningful psychiatric problems."	Study suggests efficacy of low dose amitriptyline.

RCT			12.5mg QHS vs. all placebos for 12 weeks. Doses could be increased.			
Nørregaard 1995 RCT	5.0	N = 42 with FM	Citalopram 20mg/day vs. placebo. Dose could be increased to 40mg/day.	Pain ratings decreased in both groups (citalopram decrease -1 vs. placebo -0.7), but did not differ between 2 groups.	"Citalopram showed no demonstrable effect on this group of pain patients. The very low placebo effect might indicate that the patients were not optimistic about the effect of the treatment. Many patients did not want to participate when they were informed that the test drug belonged to the group of antidepressants."	Adverse drug reactions high in both groups, e.g., headaches (24 in both groups).
Isomeri 1993 RCT	4.0	N = 45 with PFS (Yunus and Wolfe criteria used)	Amitriptyline (AT) 25mg QHS vs. cardio fitness training (CFT) vs. combined treatment for 15 weeks. Treatment begun as inpatients.	Baseline depression index scores lower in CFT group than amitriptyline or combined (9.4 vs. 12.8 and 12.2). CFT training gradually increased.	"A combination of AT and CFT is more effective in the treatment of PFS than either of these alone."	Data presented graphically.

Evidence for Norepinephrine Reuptake Inhibitor Anti-depressants (TCAs)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow -up:	Results:	Conclusion:	Comments:
Caruso, 1987 (Score=7.5)	Norepinephrine Reuptake Inhibitor Anti-depressants (TCA's)	RCT	No mention of sponsorship or COI.	N = 60 with primary fibromyalgia syndrome (PFS)	Mean age: 26 years; 8 males, 52 females.	Dothiepin 75mg QHS (n=30) – Patients received a	No follow up.	Percentage changes in tender points significant in dothiepin group (-51.5% vs. -15.8%, p <0.01). Results	"Therapy with dothiepin seems to be useful in reducing pain in patients	Authors note that further studies needed to confirm these data and

						single nighttime dose of 75 mg for 8 weeks. vs. Placebo (n=30) – Patients received a single night time dose of the placebo for 8 weeks.		for subjective pain severity also significant for dothiepin (-38.4% vs. -8.7%, p <0.01).	with PFS and shows a good tolerability with only mild and transient side effects."	"eventually to establish the appropriate dosage and length of treatment for this type of 'extra-articular rheumatism'."
Goldenberg, 1996 (Score=7.0)	Norepinephrine Reuptake Inhibitor Anti-depressants (TCA's)	RCT	Sponsored by Lot Page Fund, Ne wton-Wellesley Hospital, Newton, Massachusetts. No mention of COI.	N = 31 with Fibromyalgia (ACR criteria used)	Mean age: 43 years; 3 males, 28 females.	FL (n=22)– Patients received 20 mg of Fluoxetine in the morning and the placebo at bedtime for 6 weeks. vs. AM (n=21) – patients received the placebo in the morning and 25 mg of amitriptyline at bedtime for 6 weeks. vs.	No follow up.	Mean symptoms duration shorter among dropouts (7.26±48.1 vs. 57.0±26.1 months, p = 0.15). FIQ scores at 6 weeks: placebo 58.5±17.1 vs. amitriptyline 52.3±22.9 vs. fluoxetine 47.6±19.8 vs. combination 38.0±21.2 (p <0.03). VAS pain ratings at 6 weeks: 81.5±16.5 vs. 64.4±28.3 vs. 57.5±25.7 vs. 42.9±28.5, p <0.02.	"Both FL and AM are effective treatments for FM, and they work better in combination than either medication alone."	More dropouts on fluoxetine citing increased symptoms (3 vs. 1 in washout phase). Overall dropout rate high (38.7%).

						AM +FL (n=19) – patients received 20 mg of FL in the morning and 25 mg of AM at bedtime for 6 weeks. vs. P (n=19) – patients received the placebo in the morning and at bedtime for 6 weeks. Two-week washout phase between 4 6-week trials.				
Carette, 1986 (Score=6.5)	Norepinephrine Reuptake Inhibitor Anti-depressants (TCA's)	RCT	Sponsored by Arthritis Society. No mention of COI.	N = 59 with primary fibrositis (Smythe's criteria used)	Mean age: 40.9 years; 5 males, 54 females.	Amitriptyline 50mg (n=27) – Amitriptyline gradually increased (10mg QHS for 1 week, 25mg QHS for 2 weeks and 50mg QHS for 5 weeks). vs. placebo (n=32) - Patients	9 months.	Morning stiffness scores (baseline/5 weeks/9 weeks): amitriptyline (75±72/41±58/48±61) vs. placebo (78±71/71±80/66±76; p <0.05 for amitriptyline group compared with baseline). Pain analog scores showed similar result: amitriptyline (6.3±3.2/3.8±2.3/4.3±3.0) vs. placebo	"Our data indicate that amitriptyline is effective in relieving symptoms of fibrositis but has little effect on fibrositic point tenderness."	Baseline differences of longer symptom duration among placebo group (mean 71±58 vs. 97±87 months for placebo, p = 0.04) may have favored amitriptyline, although pain ratings somewhat higher in

						received the placebo for 8 weeks.		(5.8±2.4/5.3± 2.7/5.0±3.0) (p <0.05 for amitriptyline compared with baseline). Most in amitriptyline experienced improvements (77% at 5 weeks vs. 43% placebo; p = 0.008) while at 9 weeks, results not significant (70% vs. 50%, p = 0.11).		amitriptyline group (6.3±2.3 vs. 5.8±2.4). Sample sizes appear to have resulted in underpowered study.
Carette 1995 (6.0)	Amitriptyline	RCT	Supported by a grant from the Canadian Arthritis Society. No mention of COI.	N = 22 who met the 1990 American College of Rheumatology criteria for fibromyalgia	22 female, 0 male. Mean age 36.7±5.0 years	Amitriptyline 25 mg/day, 1 hour before sleeping or an identical-appearing inert placebo. All participants underwent both treatments.	Weeks 8 and 16	Mean scores post-treatment for amitriptyline and placebo groups, respectively – Pain: 5.07±3.22 (P<0.05 versus baseline value), 7.13±2.41 (P<0.05 versus amitriptyline tx). Fatigue 5.62±3.07 (P<0.05 versus baseline value), 7.64±1.80 (P<0.05 versus amitriptyline tx)	"The alpha NREM sleep anomaly is present in only a small proportion of patients with fibromyalgia. It does not correlate with disease severity nor is it affected by treatment with amitriptyline. A larger sample size will be needed to adequately assess the value of this sleep anomaly in predicting the response	Crossover trial. Data suggest 27% of amitriptyline group exhibited improvement compared to placebo.

									to amitriptyline."	
Heymann, R 2001 (Score = 6)	Fibromyalgia	RCT	No mention of support or COI	N = 118 fibromyalgia patients.	No mention of sex; Mean age 50.6.	Amitriptyline (N = 40) vs Nortriptyline (N = 38) vs Placebo (N = 40)	8 weeks.	FIQ post-treatment Amitriptyline (39.97 ± 6.54) Nortriptyline (48.78 ± 7.28) Placebo (51.68 ± 7.98) (p = 0.634) NTP post treatment Amitriptyline (14.2 ± 0.7) Nortriptyline (13.3 ± 0.9) Placebo (14.7 ± 0.6) (p = 0.203) NTP post treatment	"The efficacy of amitriptyline and nortriptyline was not superior to that of placebo except when analyzed by means of the verbal scale of global improvement evaluation by the patient."	Data suggest all 3 groups demonstrated improvement suggesting neither amitriptyline nor nortriptyline were superior to placebo.
Arnold, L 2010 (Score = 6)	Fibromyalgia	RCT	Sponsorship by Pfizer Inc. Dr. Arnold has received grants/research support from Allergan, Boehringer Ingelheim, Cypress Biosciences Inc., Forest Laboratories Inc., Eli Lilly and Company, Pfizer Inc., Sanofi-Aventis, and Wyeth	N = 267 patients with FM	238 females, 29 males; Mean age 50.	Esreboxetine 2 week period of 2mg/d to the max of 8mg/d (N = 134) vs Placebo (N =133) 1 week base line period, 2 week placebo period. 8 week randomized placebo controlled, 1 week follow up.	8 weeks	Esreboxetine vs placebo. Pain score change from base line. -1.55 vs -.99 (p = 0.006). FIQ score (p = 0.001) Sleep Interference Score change from baseline; -1.44 vs -.88 (p = 0.007)	"In this 8-week trial in patients with fibromyalgia, esreboxetine was associated with significant reductions in pain scores compared with placebo. It was also associated with improvements in outcomes relevant to fibromyalgia,	Data suggest at 8 weeks esreboxetine was associated with less pain and better function and less fatigue.

			Pharmaceuticals. She has been a consultant for Allergan, AstraZeneca, Boehringer Ingelheim, Cypress Biosciences, Forest Laboratories, Eli Lilly and Company, Organon, Pfizer, Sanofi-Aventis, Sepracor,Takeda, Theravance, Inc., DCB,Vivus, Inc., and Wyeth. She has served on speakers' bureaus for Forest Laboratories, Eli Lilly and Company, and Pfizer. Drs. Chatamra, Hirsch and Stoker were employees of Pfizer at the time of the study.						including the PGIC, function, and fatigue."	
Ware, M 2010 6.0	Nabilone	Crossover study.	Supported by an unrestricted grant from Valeant	N = 31 with fibromyalgia.	The mean age of the participants is 49.5	Nabilone – patients received 0.5 mg of	No follow up.	Nabilone was found to have a greater effect on sleep than	"In conclusion, we report that	Data suggests low dose of Nabilone may be an

			(Canada) Inc. No COI.		years. 5 males, 26 females.	Nabilone for two weeks. Patients then entered a washout period and received 10 mg of amitriptyline for 2 weeks vs Amitriptyline – patients received 10 mg of amitriptyline for two weeks. Patients then entered a washout period for 2 weeks and then received 0.5 mg of Nabilone.		amitriptyline on the ISI (adjusted difference -3.25; CI, -5.26 to -1.24). Based on the LSEQ sleep quality outcomes, there was no evidence of superiority of either drug, although subjects had a more restful sleep taking Nabilone compared with amitriptyline (difference -0.48; CI, 0.01 -0.95)	the synthetic cannabinoid Nabilone is an effective drug in promoting sleep in patients with FM who have chronic insomnia and may be superior to amitriptyline, which is currently widely used for this purpose. Further studies on the effects of Nabilone on sleep architecture and long term safety and efficacy in FM and other pain conditions are warranted."	effective alternative to amitriptyline for improving sleep in fibromyalgia patients.
Giraldes, A 2016 (Score = 5.5)	Fibromyalgia	RCT	Sponsorship by grant rom São Paulo Research Foundation. No mention of COI.	N = 42 patients with FM	40 females, 2 males; Mean age 44.7	Group 1 patients received 240 mg of lidocaine in 125 mL of saline Solution (N = 21) vs	8 weeks	Pain intensity; Lidocaine vs Saline T0 6.1 ± 1.3/7.2 ± 1.3 (p = 0.090) T2 4.6 ± 1.6/6.1 ± 1.7 (p = 0.010) T8 3.9 ± 2.8/2.7 ± 2.9 (p = 0.199)	"The combination of 240 mg of intravenous lidocaine (once a week for 4 weeks) with 25 mg of amitriptyline for 8 weeks	Data suggest comparable (in) efficacy between groups from pain intensity in FM patients at 8 weeks but better at 2 weeks.

						group 2 patients received 125 mL of saline, both once a week for 4 weeks (T1, T2, T3 and T4). (N = 21) All patients received amitriptyline.			had no meaningful impact in fibromyalgia patients."	
Vlainich, R 2010 (Score = 5.0)	Fibromyalgia	RCT	No mention of sponsorship or COI.	N = 30 with FM	30 females; mean age 42.8	All patients received 25 mg Amitriptyline. Group 1 received 125 mL of .09% saline. (N = 15) vs Group 2 received 240 mg lidocaine in 125 mL of .09% saline once a week for 4 weeks. (N = 15)	4 weeks	Sleep disorders G1 (T0: 15 and T4: 2) and group 2 (T0: 14 and T4: 3) Paresthesia in G1 (T0: 12 and T4: 5) and G2 (T0: 14 and T4: 3) Headache in G1 (T0: 8 and T4: 1) and G2 (T0: 9 and T4: 2) Reduction of fatigue in G1 (T0: 15 and T4: 10 patients) and G2 (T0: 15 and T4: 9 patients)	"The combination of 240 mg intravenous lidocaine (once a week) and 25 mg amitriptyline for 4 weeks did not modify pain intensity or manifestations in patients with fibromyalgia compared with amitriptyline alone."	Data suggest comparable (in) efficacy between groups.
Arnold, L 2012 (Score = 4.5)	Fibromyalgia	RCT	Sponsorship by Pfizer. COI; Dr. Arnold has received consulting fees from Eli Lilly, Cypress Bioscience,	N = 1114 patients with FM	1009 females, 105 males; mean age 50.6	Esreboxetine at dosages of 4 mg/day (N = 277), vs 8 mg/day (N = 284) 10 mg/day (N	14 weeks	LOCF difference compared to placebo, 4, 8, 10 mg/d respectively. [95% CI] –0.85, –0.24 [P =	"Esreboxetine was generally well tolerated and was associated with significant improvement	Data suggest esreboxetine at 4mg/d is sufficient to improve pain and fatigue scores such that higher

			Forest Laboratories, Takeda, AstraZeneca, Sanofi-Aventis, Gru¨nenthal, Johnson & Johnson, and Daiichi Sankyo (less than $10,000 each) and from Pfizer (more than $10,000); she has received research grants from Eli Lilly, Pfizer, Cypress Bioscience, Boehringer Ingelheim, Forest Laboratories, Novartis, and Takeda. Dr. Hirsch owns stock or stock options in AstraZeneca. Dr. Sanders owns stock or stock options in Pfizer and AstraZeneca. Drs. Ellis and Hughes own stock or stock options in Pfizer.			= 283) vs Matching placebo (N = 278) for 14 weeks.		0.001]), –0.55 (95% CI –0.85, –0.25 [P = 0.001]), and –0.22 (95% CI –0.53, 0.08 [P = 0.146]) BOCF approach difference compared with placebo. –0.36 (95% CI –0.65, –0.08 [P = 0.013]), –0.26 (95% CI –0.54, 0.03 [P = 0.075]), and –0.12 (95% CI –0.41, 0.16 [P = 0.407]). Decrease in mean pain score 4mg (p = 0.024), 8mg (p = 0.004), 10mg (p = 0.123)	s in pain, FIQ, PGIC, and fatigue scores compared with placebo. The lack of a dose-response relationship in both the efficacy and safety analyses suggests that esreboxetine at a dosage of 4 mg/day would offer clinical benefit with the least risk of drug exposure."	dosages are unnecessary. One of the most common AES was insomnia in the treatment group.

Fors, E 2001 (Score = 4.5)	Fibromyalgia	RCT	No mention of sponsorship or COI.	N = 55 patients with FM	55 females; mean age 45.7 years.	Relaxation training and guided instruction in "pleasant imagery" (PI) (n = 17) vs relaxation training and attention imagery upon the "active workings of the internal pain control systems" (N = 21) vs control group (N = 17) all patients assigned to 50-mg amitriptyline per day or placebo.	4 weeks	Differences of pain-slopes between the three psychological conditions (P=0.0001). The pleasant imagery (P<0.005), but not the attention imagery group's slope, declined when compared with the control group (P>0.05). difference between the amitriptyline and placebo slopes (main effects, P=0.98) amitriptyline psychological interaction (P=0.76)	"Pleasant imagery (PI) was an effective intervention in reducing fibromyalgic pain during the 28-day study period. Amitriptyline had no significant advantage over placebo during the study period."	Data suggest use of pleasant imagery may effective in reduction of pain associated with FM at 28 days follow-up. However data suggest amitriptyline was not better than placebo but sample size for study was relatively small.
Scudds, R 1989 (Score = 4)	Fibromyalgia	RCT	Sponsorship by the Arthritis Society Student ship and NSERC grant. No mention of CIO	N = 36 patients with fibrositis	32 females, 4 males; mean age 39.9	Amitriptyline for 4 weeks, 2 week wash out, 4 week placebo. 10 mg amitriptyline first week, 25 mg second week, and 50 mg the final 2 weeks. (N = 19) Vs Placebo First	10 weeks	Total myalgic score ($p < 0.001$), pain rating ($p < 0.01$). Total myalgic score post time vs all other times (HSD = 3.74, ($p < 0.05$)). Pain levels lower after amitriptyline than any other time. (HSD = 3.54, ($p < 0.05$)). More patients reported improvement post	"Amitriptyline was associated with significant changes on the outcome measures of pain, tender point sensitivity and patient assessment of wellbeing."	Data suggest amitriptyline improved tender point sensitivity.

						4, 2 week washout, Amitriptyline last 4 weeks. Same dosage as first. (N = 17)		amitriptyline that after placebo (x^2= = 21.6, (p < 0.001)). 8 in placebo reported some improvement.		
Carette, S 1994 (Score = 4)	Fibromyalgia	RCT	Sponsorship by grants from the Canadian Arthritis Society and Merck Frost Canada.	N = 208 patients with FM	195 females, 13 males; mean age 44.4	Amitriptyline Group; patients received 10-mg amitriptyline for first week, 25-mg 2-12th week, 50-mg last 12 weeks and cyclobenzaprine placebo. (N = 84) vs Cyclobenzaprine group. 10-mg week 1, 20 mg week 2-12, 30 mg last 12 weeks, and placebo amitriptyline.(N = 82) vs Placebo group. received both placebo. (N = 42). Amitriptyline versus placebo(P = 0.08)	6 months	At 1 month (amitriptyline, cyclobenzaprine, and placebo) 21%, 12%, and 0% had improvement. Amitriptyline vs placebo (p = 0.002) cyclobenzaprine vs placebo (p = 0.02). At 6 months 36%, 33%, 19%.	"Our data confirm the short-term efficacy of amitriptyline and cyclobenzaprine in a small percentage of patients with fibromyalgia. Long-term efficacy could not be demonstrated because of a higher than expected placebo response. Predictors of response to these drugs could not be determined. "	Data suggest no long term efficacy of either amitriptyline or cyclobenzaprine compared with placebo

						cyclobenzaprine versus placebo (P = 0.15)				

Evidence for Selective Serotonin Reuptake Inhibitors (SSRIs)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Arnold 2002 (Score = 8)	Fibromyalgia	RCT	Supported by an investigator-initiated grant from Eli Lilly and Company. No mention of COI.	N = 60 females with FM (ACR criteria used), 57% fluoxetine and 67% in placebo history of depression	60 females; mean age 46.	Titrated doses of fluoxetine (10-80mg a day, mean dose 45±25mg a day) with placebo for 12 weeks.	12 weeks	Fibromyalgia Impact Questionnaire (FIQ) scores were -8.6±14.5 in fluoxetine vs. 2.9±13.6 among placebo (p = 0.005). McGill Pain Questionnaire scores had a similar pattern (-10.8±12.3 vs. -1.8±11.9, p = 0.01).	"Fluoxetine was found to be effective on most outcome measures and generally well tolerated in women with fibromyalgia."	Dropout rates high in both groups (36.7% vs. 40.0%).
Patkar 2007 (6.5)	Paroxetine	RCT	Supported by a grant from GlaxoSmithKline. Author Krulewicz is an employee of GlaxoSmithKline and author Beebe was formerly an employee of	N = 116 who fulfilled the American College of Rheumatology diagnostic criteria for fibromyalgia	109 female, 7 male. Mean age paroxetine group 47.9 years, placebo group 49.1 years	Paroxetine controlled release (12.5-62.5 mg/day) (N = 58) vs Placebo (N = 58)	12 weeks	Survival analyses for reduction in Fibromyalgia Impact Questionnaire scores showed significantly higher proportion	"Paroxetine controlled release appears to be well-tolerated and improve the overall symptomatology in patients with fibromyalgia	Data suggest improvement in fibromyalgia symptoms via paroxetine but no significant improveme

			GlaxoSmithKline.					of paroxetine group responded (56.8%) compared to placebo (32.7%) (x^2(Breslow) = 15.75, P = .016)	without current mood or anxiety disorders. However, its effect on pain measures seems to be less robust."	nt in fibromyalgia pain.
Anderberg 2000 (5.0)	Citalopram	RCT	Supported by grants from H. Lundbeck AB, the Soderstrom Konigska Foundation, the Swedish Association of Physicians, the Marta and Nicke Nasvell Foundation, the Swedish Health Insurance System, the Uppsala County Council and 'Forenade Liv' Mutual Group Life Insurance Company, Stockholm, Sweden and the Swedish Medical Research Council (21X-9523). No	N = 35	Mean age is 48.6 years. 35 females, 0 males.	Citalopram (N = 17) vs Placebo (N = 18)	Study lasted 5 months: 4 months of treatment of either citalopram or placebo. Pain assessed every month.	Nine patients in the citalopram group and 4 in the placebo group were self-regarded as improved. The difference was not statistically significant. Depressive symptoms were decreased significantly. Sleep improved significantly in the citalopram group MADRS: -0.59 (p < 0.01) but not	"In conclusion, antidepressants like the SSRI citalopram and the SNRI venlafaxine may have beneficial effects in FMS patients."	Data suggest citalopram may reduce pain associated with FM at 2 months but diminish at 4 months.

			mention of COI.					in the placebo group MADRS: -0.39 (NS).		
Norregaard 1995 (4.5)	Citalopram	RCT	Supported by funding from H. Lundbeck A/S. No mention of COI.	N = 42	Mean age is 49 years.	Citalopram (N = 21) vs. Placebo (N = 22).	8 week treatment plan	The change in FIQ physical function was not significant in any of the groups.	"There were no trends toward improvement in the majority of parameters in any of the groups."	Data suggest lack of efficacy for FM patients.
Pae 2009 (4.0)	Paroxetine	RCT post-hoc	Supported by grant from GlaxoSmithKline. Author Krulewicz is an employee of GlaxoSmithKline.	N = 116 who fulfilled the 1990 American College of Rheumatology criteria for fibromyalgia, Visual Analogue Scale-pain score of ≥5, Beck Depression Inventory score of ≤23	109 female, 7 male. Mean age for those with history of depression/anxiety 48.1 years, those without 48.3 years	With depression/anxiety history: paroxetine dose 12.5-62.5 mg/day (N = 29) vs placebo (N = 26), Without depression/anxiety history: paroxetine (N = 29) vs placebo (N = 32)	12 weeks	Multivariate logistic regression results: history of depressive and/or anxiety do not predict treatment response (OR=0.66, 95% CI .29–1.49, Wald=0.97, (P=0.32)), drug status associated with treatment response (OR=2.57, CI 1.2–5.61, Wald=5.5, (P=0.02))	"A significant proportion of patients with fibromyalgia had a history of anxiety and or depressive disorders. However response to treatment of fibromyalgia symptoms with paroxetine CR was not associated with a history of depressive and/or anxiety disorders. Our findings need to be confirmed in more adequately-powered and well-designed subsequent studies."	Post hoc analysis with high dropout rate. Data suggest response to paroxetine appears to be independent of history of depression or anxiety.

Pae 2009 (4.0)	Paroxetine	RCT post-hoc	Supported by grant from GlaxoSmithKline. Author Pae has received research grants from Glaxo SmithKline Korea, GlaxoSmithKline and has received honoraria and is on the speaker's bureaus of GlaxoSmithKline Korea. Author Patkar is a consultant for GlaxoSmithKlin and received grant support from GlaxoSmithKline. Author Krulewicz is an employee of GlaxoSmith-Kline. Author Masand is on the speaker's bureaus of GlaxoSmithKline.	N = 112 who fulfilled the 1990 American College of Rheumatology criteria for fibromyalgia, Visual Analogue Scale-pain score of ≥5, Beck Depression Inventory score of ≤23	106 female, 6 male. Mean age for those with history of abuse 47.0 years, those without 48.6 years	Those with history of abuse (N = 59) vs those without history of abuse (N = 53). In original study there were two randomized groups of placebo and paroxetine	12 weeks	No significant difference in number of responders defined as ≥25% reduction in FIQ-total score between those with history of abuse (n=22, 37.2%) or without (n=26, 49.1%) (Fisher's exact test P=0.49). No significant differences in proportion of responders with or without history of abuse in the paroxetine CR (abuse n=16, 53.3%; no abuse n=14, 46.7%, Fisher's exact test, P=0.48) or in the placebo groups	"Although, a significant proportion of patients with fibromyalgia reported a history of abuse, it does not appear to have any significant clinical correlates at baseline. History of abuse did not predict response to treatment in patients with fibromyalgia participating in a controlled trial of paroxetine controlled release."	Data suggest history of abuse did not predict response to treatment with paroxetine.

								(abuse n=7, 38.9%; no abuse n=11, 61.1%, Fisher's exact test P=0.16). Multivariate logistic regression showed history of abuse did not predict treatment response (OR=1.16, P=0.35), while the drug status significantly associated with treatment response (OR=2.51, P=0.02)		

Evidence for Serotonin Receptor Antagonists

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Matthey, 2013 (score=7.5)	Fibromyalgia	RCT	No COI and sponsored by Pierre Fabre Médicament.	N=80 patients	Mean age: 49.7 years; 0 males, 80 females.	MLN group: received (100, 150, 200mg/day (n=38) vs PBO group: placebo	7 weeks	MLN patients reported significant reduction in pain compared to placebo group (p=.03). Change in pain reduction between MLN 200	"Milnacipran has a predominantly supraspinal analgesic effect as evidenced by the significant clinical benefits	Data suggest MLN reduced pain in FM patients and higher doses increased pain reduction.

						group (n=39)		and placebo was -18.4mm [-30.9, -5.8] (p=.02). At week 7, PGR responder rate was 59.4% for MLN group compared to placebo at 34.2% (p=.04). Ninety percent of MLN patients showed 10 mmHg increase in blood pressure compared to placebo 38% (p<.01). Heart rate was increased 10 beats per minute in 82% of MLN group and 28% for placebo (p<.01).	and the absence of changes in the nociceptive spinal reflex threshold. Higher dose was associated with higher pain reduction."	
Arnold 2004 (7.5)	Duloxetine	RCT	Supported by Eli Lilly and Company. Authors Crofford and Arnold received consulting fees or honoraria in the last 2 years from Eli Lilly and Company Author Goldstein's wife is employed by Eli Lilly and Company.	N = 207 with FM, 88.9% females, 38.2% had current major depressive episode	184 female, 23 male. Mean age placebo 48.3 years, duloxetine group 49.9 years	Duloxetine (N = 104) vs placebo (N = 103) for 12 weeks. Duloxetine increased at 20mg/day increasing to 60mg/day.	12 weeks	Differences in improvements in fibromyalgia impact scores: -4.52, p = 0.042. Females responded more than males in FIQ scores (p = 0.029).	"Duloxetine was an effective and safe treatment for many of the symptoms associated with fibromyalgia in subjects with or without major depressive disorder, particularly for women, who had significant improvement across most outcome measures."	Other psychiatric disorders unclear and depressive symptoms not described. Dropouts high in acute phase, higher in duloxetine (44%) than placebo (36%). More prior anti-depressant use in placebo group.

Arnold 2005 (7.5)	Duloxetine	RCT	Sponsored by Eli Lilly and Company. No mention of COI.	N = 354 females with FM	354 female, 0 male. Mean age 49.6 years	Duloxetine 60mg QD (N = 118) vs 60mg BID (N = 116) vs. placebo (N = 120)	12 weeks	Response rates were 33% placebo vs. 55% daily dose vs. 54% twice daily dose groups.	"Both duloxetine 60mg QD and duloxetine 60mg BID were effective and safe in the treatment of fibromyalgia in female patients with or without major depressive disorder."	Dropout rates elevated in placebo (43%) and duloxetine (35% and 39%). Data suggest no significant differences in efficacy between active treatment arms. Adverse effects somewhat higher in duloxetine.
Lee, 2016 (score=6.5)	Rheumatoid Arthritis	RCT	Sponsored by Harvard University and its affiliated academic health care centers	N=43 subjects	Mean age: 54.01 years; 7 males, 25 females.	Milnacipran first group A: received milnacipran for 6 weeks followed by 3 week wash out, then 6 weeks of placebo (n=17) vs Placebo first group B: received 6 weeks of placebo, 3 weeks of wash-out, then 6 weeks of milnacipran. (n=15)	15 weeks	Group A Brief Pain Inventory pain intensity score decreased by .67 points (95% CI -1.29, -0.04) compared to Group B decreasing by .28 points (95% CI -0.9, 0.35). This was not statistically significant (p=.37).Mean symptom intensity scale score decreased by .71 points for Group A (95% CI -1.33, -0.07) and .80 points for Group B (95% CI -1.43, -0.17). Pain threshold increased by 0.75	"Compared to placebo, milnacipran did not improve overall, self-reported pain intensity among subjects with widespread pain taking stable RA medications."	Crossover trial. Data suggest each of efficacy.

								(95% CI 0.19, 1.31) for Group A and 0.08 (95% CI -0.49, 0.64) for Group B. Brief pain inventory pain intensity score decreased by 1.05 points for Group A compared to an increase .09 points during placebo. Most common adverse effects for milnacipran were nausea (25.8%), loss of appetite (9.7%), insomnia (7.3%), and vomiting (7.3%).		
Clauw, 2008 (score=6.0)	Fibromyalgia	RCT	Sponsored by Forest Research Institute, Inc., Jersey City, New Jersey and Cypress Bioscience, Inc., San Diego, California. Conflict of interest with author financial compensation from supporting groups and position in pharmaceutical company.	N=1196 patients with fibromyalgia	Mean age: 50.2 years; 45 males, 1151 females.	Milnacipran 100 mg/d group: (n=399) vs Milnacipran 200 mg/d group (n=396) vs Placebo group: (n=401)	3 months	Significantly more patients treated with milnacipran met all 3 criteria for FM composite response compared to placebo (MLN 100 mg/d, p=.01, MLN 200 mg/d, p=.02). Milnacipran groups showed greater proportions of FM composite responders compared to placebo (MLN 100 p=.002, MLN 200 p<.001) and FM pain composite responders (MLN	"In these adult patients with FM, both doses of milnacipran (100 mg or 200 mg) were associated with significant improvements in pain and other symptoms."	Data suggest patients receiving either 100 mg/d or 200mg/d of milnacipran experienced improvement in pain and other symptoms.

								100 p=.001, MLN 200 P<.001). Significant reduction in pain was observed after 1 week for both milnacipran groups compared to placebo (MLN 100 p=.004; MLN 200 p=.04). OC analysis patients rating improvement was 48.3% for MLN 100, 51% for MLN 200, and 32.9% for placebo. Rating for worsening condition was 9.5% for MLN 100, 6.3% for MLN 200, and 13.8% for placebo (MLN 100 p=.001), MLN 200 p<.001). Significant improvement for MLN 200 relative to placebo was achieved in SF-36 MCS (p=.045), where it was not comparing MLN 100 with placebo.		
Arnold 2010 (6.0)	Duloxetine	RCT	No mention of COI or sponsorship.	N = 530 diagnosed with fibromyalgia according to the American	494 female, 36 male. Mean age duloxetine group 50.7 years,	Duloxetine group - 60 mg/day (N = 263) vs Placebo (N = 267)	12 weeks	Patient Global Impression of Severity scores at week 12: duloxetine 2.8, placebo 3.4 (P <	"Treatment with duloxetine 60, 90, and 120 mg/day was associated with feeling much	High dropout rate. Data suggest fibromyalgia patients treated with

				College of Rheumatology criteria, scored ≥ 4 on the average pain item of the Brief Pain Inventory (BPI; modified short form)	placebo group 49.6 years			0.001). Least squares mean change from baseline for duloxetine and placebo, respectively: Clinical Global Impression of Severity -1.2, -0.8 (P < 0.001), Brief Pain Inventory -2.3, -1.5 (P < 0.001), Cognitive and Physical Functioning Questionnaire -5.3, -4.2 (P = 0.051).	better, pain reduction, being less bothered by sleep difficulties, and improvement in mood, stiffness, fatigue and functioning."	duloxetine had less pain, better mood, sleep, less fatigue and stiffness than placebo.
Arnold 2011 (6.0)	Duloxetine	RCT	Supported by Lilly USA, LLC. In the past 12 months, author Arnold received grants/research support from Eli Lilly and Company, Pfizer Inc., Cypress Bioscience, Inc., Boehringer Ingelheim, and Forest Laboratories, Inc., and honoraria as a consultant to Eli Lilly and Company, Pfizer Inc., Cypress	N = 530 diagnosed with fibromyalgia according to the American College of Rheumatology criteria, scored ≥ 4 on the average pain item of the Brief Pain Inventory (BPI; modified short form)	494 female, 36 male. Mean age 50.2 years	Duloxetine 60-120 mg/day (N = 263) vs Placebo (N = 267)	Weeks 12 and 24	Mean change in multidimensional fatigue inventory ratings in pain responders and non-responders (general fatigue, mental fatigue, physical fatigue, reduced activity, and reduced motivation, respectively): Duloxetine Responders -3.4, -3.0, -3.1, -2.6, -2.7. Placebo Responders -2.8, -1.8, -2.7, -1.7, -1.6. Duloxetine Non-responders -0.7, -0.9, -0.6, -0.2, -0.6. Placebo	"Treatment with duloxetine significantly improved multiple dimensions of fatigue in patients with fibromyalgia, and improvement was maintained for up to 24 weeks."	Data suggest at 24 weeks fibromyalgia patients treated with duloxetine had decreased fatigue.

			Bioscience, Inc., Boehringer Ingelheim, Forest Laboratories, Inc., Allergan, Takeda, UCB, Theravance, AstraZeneca, Sanofi-Aventis, and Grünenthal. Author Wang is a former employee and authors Ahl, Gaynor, and Wohlreich are current employees of and stockholders in Lilly USA, LLC.					Non-responders -0.4, -0.5, -0.3, 0.2, -0.4.		
Jensen, 2014 (score=5.5)	Fibromyalgia	RCT	No COI, sponsored by Pierre Fabre. E.C. acknowledges financial support from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St	N=92 patients	Mean age = 44 yrs.:0 males, 92 females.	Milnacipran responders (n=21) vs Placebo responders (n=16)	12 weeks	Milnacipran responders had significantly higher brain activity in posterior cingulum after treatment compared to placebo responders (t=3.99, MNI coordinates x = _4, y = _30, z = 46). An ANOVA was performed in SPSS and revealed significant	"There was also significantly reduced sensitivity to experimentally evoked pressure pain in milnacipran responders, an antihyperalgesic effect that was not seen in placebo responders."	Data suggest different mechanisms for treatment responses to either milnacipran or placebo in FM patients as short pain history patients with FM had a positive response to milnacipran.

			Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. K.B.J. receives support from the COFAS Marie Curie Fellowship and Osher Center for Integrative Medicine at Karolinska Institutet. E.K. received support from the Swedish Rheumatism Association.					effect for treatment, (F(1, 24) = 6.5, P < .05). Milnacipran responders showed increased activity in the posterior cingulum after treatment compared to placebo responders. Significant correlation was observed between the degree of improvement of experimental pain (P50) and posterior cingulum signal intensity after treatment in milnacipran responders (P = .04, 2-tailed) but not in placebo responders (P = .09, 2-tailed). Milnacipran responders showed increased activity in the posterior cingulum after treatment compared to milnacipran nonresponders (t = 3.97; MNI coordinates x =		

								10, y = _28, z = 46). No Significant results were observed for multiple comparisons. There was a trend toward increased activations in the left lateral prefrontal cortex in nonresponders (t = 3.5; MNI coordinates x = _34, y = 44, z = 16).		
Ahmed, 2015 (score= 5.5)	Fibromyalgia	RCT	No COI. Sponsored by Forest Research Institute, Jersey City, NJ.	N=19 subjects with fibromyalgia	Mean age: 49.2 years; 2 males, 17 females.	All participants received placebo and milnacipran.	4 weeks	Significant pain reduction for milnacipran compared to placebo was (end of treatment paired difference: −1.44; *t*9 [p value] = −2.350 [0.043]). No significant improvements for MLN group was observed in WASO and NAASO, but showed reduced SE (p=.049).	"The data suggest that milnacipran is not sedating in most patients with fibromyalgia and improvements in sleep are likely a result of pain improvement."	Small sample crossover study. Data suggest lack of efficacy with a trend towards improved sleep in some FM patients.
Trugman, 2014 (score=5.5)	Fibromyalgia	RCT	Sponsored by Forest Laboratories Inc. as well as Cypress Bioscience Inc. Conflict of interest with J.M.T., R.H.P. and Y.M. as full-	N=321 patients with fibromyalgia	Mean age: 48.6±10.6 years; 8 males, 173 females.	Milnacipran: (n=210) vs Placebo: (n=111)	4 and 7 weeks	Two weeks after stopping medication, the mean change from baseline in sitting SBP decreased by 27% (þ5.39mmHg at Week 5). Mean sitting DBP and	"Fibromyalgia patients receiving milnacipran in this ABPM study had mean increases in blood pressure and heart rate that	Data suggest milnacipran elevated blood pressures and heart rates of FM patients.

			time employees, CMRO peer reviewers may have received honoraria for their work.					heart rate decreased by 55% and 74% (þ5.23mmHg at Week 5 for DBP; þ14.01 bpm at Week 7 for heart rate), respectively. AEs were 81% and 73.9% for milnacipran and placebo. Milnacipran showed increased vital signs. Nausea was most common AE with milnacipran group.	were consistent with those observed in clinical efficacy trials. Diurnal variation was preserved and changes were not greater in hypertensive patients than in non-hypertensive patients."	
Clauw, 2013 (score=5.0)	Fibromyalgia	RCT	COI: DJC has received grants and research support from Pfizer Inc and Forest Laboratories. He has been a consultant for and has served on advisory boards for Pfizer Inc, Eli Lilly and Co, Forest Laboratories, Inc, Cypress Bioscience, Inc (now Royalty Pharma), Pierre Fabre Pharmaceuticals, UCB and	N=151 patients with fibromyalgia	Mean age: 54.3±9.0 years; 6 males, 144 females.	Milnacipran group: (n=100) vs Placebo group: (n=50)	4 weeks	Average time to LTR for placebo was 56 days and 50% milnacipran group did not experience LTR. Sixty-four percent of patients switched to placebo experienced an LTR compared with 35% of patients who continued with milnacipran. Eighty-one patients in milnacipran group maintained 30% or more pain improvement and 58% in placebo	"Continuing efficacy of milnacipran was demonstrated by the loss of effect following withdrawal of treatment in patients who received an average of 3 years of milnacipran treatment."	Data suggest continuing long term milnacipran efficacy in patients who, on average, received milnacipran for approximately 3 years and then had milnacipran withdrawn.

			AstraZeneca. PJM has received research and grant funding as well as consultation fees from Forest Laboratories, Inc, Cypress Bioscience, Inc, Eli Lilly and Co, Pfizer Inc, Allergan, Inc, Wyeth Pharmaceuticals, Jazz Pharmaceuticals and Fralex Therapeutics. In addition to being full-time employees of Forest Research Institute, Inc, a wholly owned subsidiary of the study sponsor (Forest Laboratories, Inc), RHP, JMT and YW hold stock in the parent company. No mention of sponsorship.					group (95% CI, 0.19, 0.65; p<.001).		
Gendreau, 2005 (score=5.0)	Fibromyalgia	RCT	Sponsored by Cypress Biosciences,	N=125 patients with fibromyalgia	Mean age: 47.0±11.1 years; 3	Milnacipran BID: received	3 months	BID group showed more effective results than QD	"In this Phase II study, milnacipran led	Phase II study. Data suggest milnacipran led

			San Diego, California. Drs. COI: M. Gendreau, J. Gendreau, and J. Kranzler are employees of Cypress Biosciences. Drs. Clauw, Gracely, and Williams are paid consultants for and shareholders in Cypress Biosciences. Drs. Mease and Thorn are consultants for Cypress Biosciences.		males, 122 females.	milnacipran twice daily (n=51) vs Milnacipran QD: received milnacipran once daily (n=46) vs Placebo: (n=28)		group. Improvement for pain was only significant for BID group for 9 of 13 pain measures and 0 in the QD group. Greater pain reduction was observed in non-depressed patients treated with milnacipran compared to depressed patients. Milnacipran groups were more likely to report improvement more than the placebo (73% BID, 77% QD, 38% placebo; p=.013 BID vs QD; p=.008 for QD vs placebo). BID group showed significant improvements in pain (p=.032), fatigue (p=.032), and morning stiffness (p=.047) compared to placebo.	to statistically significant improvements in pain and other symptoms of FM. The effect sizes were equal to those previously found with TCA, and the drug was generally well tolerated."	to statistically significant pain reduction.
Mease, 2009 (score=5.0)	Fibromyalgia	RCT	Supported by Forest Laboratories, Inc., New York, New York, and Cypress	N=888 patients with fibromyalgia	Mean age: 49.43 years; 39 males, 849 females.	Milnacipran 100 mg/d: (n=224) vs Milnacipran 200 mg/d: (n=441) vs	3 months	Higher percentage of patients in milnacipran groups met FM criteria as composite	"Milnacipran is safe and effective for the treatment of multiple	High dropout rate (42.3%) making conclusions different.

			Bioscience, Inc., San Diego, California, USA. COI: Dr. Mease has received research grant support from Pfizer Inc, Cypress Bioscience, Inc., Forest Laboratories, Inc., Eli Lilly and Company, Allergan, Wyeth Pharmaceuticals, Jazz Pharmaceuticals, and Fralex Therapeutics. Dr. Clauw has received grant support from Cypress Bioscience, Inc. and serves as a consultant to Cypress Bioscience, Inc, Forest Laboratories, Inc., Pierre Fabre Médicament, Pfizer Inc, Eli Lilly and Company, Wyeth Pharmaceuticals, and Proctor			Placebo: (n=223)		responders compared to placebo (MLN 200, p=.017; MLN 100, p=.028). FM pain composite responder rate for MLN 200 group observed statistical significance compared to placebo using BOCF/LOCF (25.6% vs 18.4%, p=.034). Pain improvements were similar for both MLN groups, but size of 100 mg group decreased significance detection. Significant pain reduction was observed after 1 week for MLN groups compared to placebo. Physical functioning, bodily pain, and mental health showed significant improvement for MLN 200 group (p=.026; p=.003; p=.008; respectively). Improvement in fatigue and cognition were	symptoms of FM."	

			and Gamble. Dr. Mease was an investigator of this study and a consultant; Dr. Clauw was a consultant for this study. As consultants, Drs. Mease and Clauw were involved in the study design, analysis of results, and preparation of the manuscript. Drs. Gendreau, Rao, and Kranzler are employees of Cypress Bioscience, Inc. Drs. Chen and Palmer are employees of Forest Laboratories, Inc.					observed for MLN 200 group compared to placebo at 27 weeks (p=.035, p=.016, respectively). Most common AE were nausea and headache.		
Murakami 2012 (5.0)	Duloxetine	RCT	Supported by Shionogi & Co. Ltd., Eli Lilly Japan K.K., and Eli Lilly & Company. Authors Murakami and Osada are employees of Shionogi & Co. Ltd. Author Alev	N = 386 diagnosed with fibromyalgia according to the 1990 American College of Rheumatology criteria, had a Brief Pain Inventory	321 female, 65 male. Mean age for placebo group 49.5 years, duloxetine group 47.8 years	Duloxetine 60 mg/day (N = 191) vs Placebo (N = 195) for 14 weeks	1 week after final treatment	Brief Pain Inventory score differences between placebo and duloxetine: MMRM -0.32 (P = 0.0988), LOCF -0.38 (P = 0.0408), BOCF -0.45 (P = 0.0132), WOCF -0.47 (P = 0.0132). Post hoc BOCF	"These results suggest that duloxetine treatment could be associated with improvements in pain relief and QoL in Japanese patients with fibromyalgia."	Data suggest primary measures do not support efficacy versus placebo.

			is an employee of Eli Lilly Japan K.K. No non-financial competing interests to declare.	average pain score ≥4				and WOCF analyses showed change in average pain score significantly greater in duloxetine group (both P = 0.0132)		
Russell 2008 (5.0)	Duloxetine	RCT	Sponsored by Eli Lilly and Company and Boehringer Ingelheim GmbH. Authors Chappell, Detke, Kajdasz, Walker, and Wohlreich are employees and stockholders of Eli Lilly and Company.	N = 520 diagnosed with fibromyalgia according to the American College of Rheumatology, average pain severity item score ≥4 on Brief Pain Inventory	493 female, 27 male. Mean age for duloxetine 20 mg/day 50.9 years, 60 mg/day 51.8 years, 120 mg/day 51.1 years, placebo 50.3 years	Duloxetine 20 mg/day (N = 79) vs Duloxetine 60 mg/day (N = 150) vs Duloxetine 120 mg/day (N = 147) vs placebo (N = 144)	3 and 6 months after initial treatment	3 month linear squares mean change for duloxetine 20 mg/day, 60 mg/day, 120 mg/day, and placebo, respectively: BPI average pain severity score -1.92, -1.99 (P ≤ 0.05 vs placebo), -2.31 (P ≤ 0.001), -1.39. PGI-I score 2.85 (P ≤ 0.01), 3.04 (P ≤ 0.05), 2.89 (P ≤ 0.01), 3.39.	"Study results demonstrated that duloxetine at doses of 60 mg/day and 120 mg/day appears to be safe and efficacious in patients with fibromyalgia."	High dropout rate. Data suggest duloxetine administered to fibromyalgia patients in doses of either 60 mg/day or 120 mg/day may be effective for up to 6 months.
Saxe, 2012 (score=4.5)	Fibromyalgia	RCT	Sponsored by Forest Laboratories, Inc., New York, New York, and Cypress Bioscience, Inc., San Diego, California, USA. COI: P.A.S. has received consulting fees from Forest Laboratories Inc.	N=178 patients	Mean age: 49.17 years; 33 males, 682 females.	MLN/MLN: received milnacipran 100 mg/d for 12 weeks (n=178) vs MLN/PBO: received milnacipran for 2 weeks, then were re-randomized to receive	14 weeks	Worsening VAS pain scores were observed within 1 week after discontinuing milnacipran. At discontinuation phase, MLN/PBO group showed greater loss of therapeutic improvements than MLN/MLN group (p<.05). Proportion of	"Patients discontinuing milnacipran experienced worsening in multiple efficacy parameters within 2 weeks. Vital sign changes observed with milnacipran during the 12-week stable-	Data suggest the discontinuation of milnacipran worsened FM symptoms within 2 weeks.

			(5$15,000). L.M.A. has received consulting fees, and/or honoraria from Gru¨nenthal, Forest Laboratories Inc., Daiichi Sankyo (5$10,000 each) and Pfizer Inc (4$10,000). She has received research support from Eli Lilly and Company, Cypress Bioscience Inc., Boehringer Ingelheim GmBH, Forest Laboratories Inc., Novartis AG, Takeda Pharmaceutical Company Ltd, and Pfizer Inc. R.H.P. and W.C. are full-time employees of Forest Research Institute Inc., a subsidiary of Forest Laboratories Inc. and own stock in that company.			placebo for 10 weeks (n=178) vs PBO/PBO: received placebo for 12 weeks (n=359)		responders continued to be significantly higher in patients previously treated with milnacipran compared to placebo, regardless if remaining on milnacipran or switching to placebo. Difference in 3 measure responders between MLN/MLN group and MLN/PBO was significant (32.3%, 22%, p=.034 respectively). Increase in blood pressure, and heart rate was observed for MLN groups. Adverse events were lower in patients who discontinued MLN treatment (16.3%) than continued MLN (18.0%), or placebo (19.2%).	dose period decreased or returned to baseline values within 2 weeks after discontinuation of treatment."	

			R.M.G. was formerly an officer and shareholder in Cypress Bioscience Inc. CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.							
Branco, 2010 (score=4.5)	Fibromyalgia	RCT	Sponsored by Pierre Fabre Médicament, Boulogne, France. Dr. Branco has received grant support as an investigator and consultant for Pierre Fabre Médicament. Drs. Zachrisson and Perrot have served as speakers and consultants for Pierre Fabre Médicament. Dr. Mainguy is an employee	N=884 patients with fibromyalgia	Mean age: 48.76 years; 50 males, 826 females.	Milnacipran 200 mg/d: (n=430) vs Placebo: (n=446)	17 weeks	At 1-year extension, proportions of composite responders were 27.5% (PBO: MLN100), 31.5% (PBO: MLN150), and 32.2% (PBO: MLN200), and 35.9% (MLN200:MLN200). After 1-year extension, improvement in pain, fatigue, and sleep was observed for all MLN doses. Most common AE was hyperhidrosis and nausea.	"Milnacipran is an effective and safe treatment for pain and other predominant symptoms of FM."	Data suggest milnacipran improved pain as well as other symptoms associated with FM.

			and shareholder of Pierre Fabre Médicament. Medical writing assistance provided by Prescott Medical Communications Group was supported by Pierre Fabre Médicament.							
Arnold, 2010 (score=4.5)	Fibromyalgia	RCT	Sponsored by Forest Laboratories, Inc. 1Lesley M. Arnold, MD: University of Cincinnati College of Medicine, Cincinnati, Ohio; 2R. Michael Gendreau, MD, PhD, Judy F. Gendreau, MD: Cypress Bioscience, Inc., San Diego, California; 3Robert H. Palmer, MD, Yong Wang, PhD: Forest Research Institute,	N=1025 patients with fibromyalgia	Mean age: 48.9 years; 48 males, 977 females.	Milnacipran 100 mg/day: (n=516) vs Placebo: (n=509)	12 weeks	Pain assessments all revealed significant improvements following treatment of milnacipran compared to placebo. Significant reduction in mean pain scores was observed in milnacipran group compared with the placebo during second weeks of dose-escalation ($p<0.001$) until end of 12 week trial. The same was observed for greater overall improvement on the PGIC. Milnacipran 100 mg/d significantly reduced fatigue	"Milnacipran administered at a dosage of 100 mg/day improved pain, global status, fatigue, and physical and mental function in patients with fibromyalgia."	Data suggest a dose of 100 mg of milnacipran/day (50 mg bid) improves pain, fatigue, mental and physical function in FM patients.

			Inc., Jersey City, New Jersey. COI: Dr. Arnold has received consulting fees, speaking fees, and/or honoraria from Cypress Bioscience, Wyeth, Boehringer Ingelheim, Allergan, Takeda, UCB, Theravance, AstraZeneca, and Sanofi-Aventis (less than $10,000 each) and from Eli Lilly, Pfizer, and Forest Laboratories (more than $10,000 each) and has received research support from Eli Lilly, Cypress Bioscience, Wyeth, Boehringer Ingelheim, Allergan, Forest Laboratories, and Pfizer. Drs. R. M. Gendreau and J. F. Gendreau own					compared to placebo (p=.036) and depression (p=.008). Most common reported adverse event was nausea.		

			stock or stock options in Cypress Bioscience. Drs. Palmer and Wang own stock or stock options in Forest Laboratories.							
Schmidt-Wilcke, T 2014 (Score = 4.5)	Fibromyalgia	RCT	Sponsorship by Forest laboratories. COI Authors Ichesco, Hampson, Kairys, and Peltier, have no financial relationships to disclose. Dr. Clauw has consulted for Forest Laboratories, Pfizer, Inc., Cerephex Corporation, Eli Lilly and Company, Merck & Co., Nuvo Research Inc., Tonix Pharmaceuticals, Johnson & Johnson, Pierre Fabre, Cypress Biosciences, Wyeth Pharmaceuticals,	N = 15 patients with fibromyalgia	15 females; mean age 40.7	Milnacipran, (MLN) Dose escalation of MLN up to 200 mg/day vs Placebo	8 weeks	BPI Sev change; MLN: mean = −0.88 (p = 0.076); PBO: mean = −0.17 (p = 0.78); BPI Int change; MLN: mean = −1.1, (p = 0.03); PBO: mean = −0.56 (p = 0.31). MLN vs Placebo (BPI Sev: p=0.39, BPI Int: p=0.50). rs-fc of the right PAG seed and the right mid-IC, and subsequent reduction in clinical pain severity (BPI Sev; MLN: r = 0.885, (p < 0.001); placebo: r = –0.216, (p = 0.440)	"Overall we were able to show that rs-fc patterns of brain structures involved in antinociception and pain modulation might be useful parameters for the prediction of treatment response to the SNRIMLN in fibromyalgia patients. As in clinical practice only a subset of patients respond to pharmacological treatment, such approaches might turn out useful tools to identify subgroups of patients likely to respond to	Data suggest the anterior cingulate cortex and insular cortex connectivity may be a component of milnacipran and fcMRI may be useful for prediction treatment response.

			UCB, AstraZeneca, Jazz Pharmaceuticals, Abbott Laboratories, and Iroko Pharmaceuticals. Dr. Harris has consulted for Pfizer, Inc. Dr. Harte has consulted for Pfizer, Inc. and analgesic Solutions. Dr. Schmidt-Wilcke was supported by a grant of the DFG						one or the other approach moving towards an individualized medicine. Further research is needed to both confirmand extend our findings."	
Mease, 2013 (n=4.5)	Fibromyalgia	RCT	Sponsored by Forest Laboratories, Inc. Conflict of interest:	N=364 patients with fibromyalgia	Mean age: 49.4 years; 33 males, 319 females.	Pregabalin: (n=178) vs Pregabalin and Milnacipran: (n=179)	4 and 12 weeks	Responders reported improvement for MLN+PGN at 46.4% compared to PGN only at 20.8% (p<.001). Patients with at least 30% pain improvement was higher in MLN+PGN group than in PGN alone (45.8%, 19.7% respectively). Mean improvement from randomization VAS pain score was significantly greater in	"In this exploratory, open-label study, adding milnacipran to pregabalin improved global status, pain, and other symptoms in patients with fibromyalgia with an incomplete response to pregabalin treatment."	Open label study suggesting the addition of milnacipran to pregabalin improved pain and overall global outcomes in FM patients who did not have a complete response pregabalin alone.

								MLN+PGN group (±SEM) -20.77 (±1.92); PGN -6.43 (±1.93); p<.001. Significant differences in groups was observed at 2 weeks (P<.001). Most common AE with milnacipran and pregabalin were nausea (12.5%), fatigue (10.3%), and constipation (9.8%).		
Branco, 2011 (score=4.0)	Fibromyalgia	RCT	Sponsored by Pierre Fabre Médicament, Boulogne, France. COI: Dr. Branco has received grant support as an investigator and consultant for Pierre Fabre Médicament. Dr. Cherin has received grant support as an investigator and speaker for Pierre Fabre Médicament. Drs. Montagne and Bouroubi are employees	N=468 patients with fibromyalgia	Mean age: 49.7±9.4 years; 30 males, 438 females.	Milnacipran: 200 mg/d (n=430) vs Placebo: (n=446)	1 year	Significant improvement was observed in response rate (pain VAS+PGIC) in FAS for milnacipran 200 group compared to placebo LOCF (OR 1.90, 95% CI 1.34-2.68, p=.0003). Overall improvement in multidimensional functioning between milnacipran and placebo. SF-36 PCS (0.98; p=.025), SF-36 MCS (1.45; p=.007), and other SF-36 domains. Milnacipran significantly	"Over 1 year, milnacipran 100, 150, and 200 mg/day exhibited sustained and safe therapeutic effects on predominant symptoms of FM."	One-year extension study. Data suggest at 1 year MLN doses of either 100, 150, or 200 mg/d showed sustained therapeutic effects for FM patients.

			of Pierre Fabre Médicament.					reduced fatigue (p=.006), cognition (p=.041), and quality of sleep (p=.007). Most common AEs were nausea, headache, and hyperhidrosis.		
Goldenberg, 2010 (score=4.0)	Fibromyalgia	RCT	No COI and sponsored by Forest Laboratories, Inc., New York, New York and Cypress Bioscience, Inc., San Diego, California.	N=449 patients with a diagnosis of fibromyalgia	Mean age: 49.68 years; 14 males, 438 females.	MLN 200: received 200 mg/d of milnacipran (n=441) vs MLN 100: received 100 mg/d of milnacipran (n=224) vs Placebo (n=223)	6 months	At end of 1 year, patients treated with MLN showed improvement in pain, regardless on MLN for entire period or re-randomized to placebo. Improvement in pain was 46.7% for MLN group for 1 year and 47.2% for PBO/MLN. General improvement was observed for MLN groups. Mean PGIC scores were same for patients on 1 year of MLN (2.2, 95% CI 2.0-2.4) and for placebo to MLN group (2.2, 95% CI 1.9-2.5). Most common AE was nausea for MLN groups.	"In addition to confirming that milnacipran safely and effectively improves the multiple symptoms of fibromyalgia, these data indicate that milnacipran provides 1-year durable efficacy in this patient population."	Data suggest milnacipran sustained pain reduction up through 12 months.
Ang, 2013 (score=4.0)	Fibromyalgia	RCT	No COI and sponsored by National Institute of	N=58 patients with fibromyalgia	Mean age: 46.59±10.39 years; 4	Combination therapy (n=20) vs milnacipran	9 weeks, 21 weeks.	Combination therapy showed improving SF-36 physical function	"In this pilot study, a therapeutic approach that	Data suggest combination therapy (CBT was

			Arthritis and Musculoskeletal and Skin Diseases (Grant number: 1R21AR056046-01A2).		males, 54 females	and education (n=19) vs placebo and combinatio n therapy (n=19)		(SE=9.42(5.48) p=.09) and in reducing weekly average pain intensity (SE=-1.18(.62) p=.07). Dropout rate was 15%. Eighty-nine percent of subjects completed 6/8 phone-based therapy sessions.	combines phone-based CBT and milnacipran was feasible and acceptable. Moreover, the preliminary data supports conducting a fully powered RCT."	milnacipran) was better than other 2 groups for pain reduction and improving physical function.
Chappell 2008 (4.0)	Duloxetine	RCT	Supported by Eli Lilly and Co and Boehringer Ingelheim. Author Chappell is an employee of the Lilly Research Laboratories, Eli Lilly and Co.	N = 350 diagnosed with fibromyalgia according to the American College of Rheumatolog y criteria	335 female, 15 male. Mean age 49 years	Duloxetine 60 mg/day (N = 104) vs 120 mg/day (N = 203)	52 weeks after initial treatmen t	Least squares mean change in BPI average pain scores: Duloxetine 60 mg/day -0.37, 120 mg/day -0.16 (P > 0.05)	"The profile of duloxetine for the long-term treatment of fibromyalgia was consistent with that seen in other indications for which the drug is currently marketed."	High dropout rate.

Evidence for Noradrenergic and Specific Serotonergic Antidepressants

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Miki 2016 (7.0)	Mirtazapine	RCT	Funded by Meiji Seika Pharma Co, Ltd. No COI.	N = 422	Mean age is 45.15 years; 347 males, 75 females.	Mirtazapine (N = 215) vs Placebo (N =215)	12-week double blind treatment period with 3-10 visits.	Using the NRS pain score, the mirtazapine group score reduced by 1.61 compared with the placebo group reduced by 1.17 (P = 0.0018). The amount of weeks used increased the difference between	"Mirtazapine was found to be effective in controlling FM pain even in patients without coexisting depression, indicating the independence of this	Data suggest patients treated with Mirtazapine reported less post treatment pain and improved quality of life when

								the two groups. Week 6 (P = 00192), week 8 (P = 0.0192), week 10 (P = 0.0036), week 12 (P = 0.0013). Using JFIQ scores, the mirtazapine group reduced by 12.93 compared with the placebo group reduced by 9.29 (P = 0.0097). Significant difference at week 8 (P = 0.0042) and week 12 (P = 0.0032).	drug's anti-FM efficacy from its antidepressant effect. The drug was tolerated well in Japanese patients with FM, having a safety profile similar to that reported in Japanese patients with depression. A further confirmatory study should be designed to establish its benefit for the treatment of FM."	compared to placebo.
Yeephu 2013 (7.0)	Mirtazapine	RCT	Supported by a scholarship from the Commission on Higher Education Staff Development Project for the Joint PhD Program in Biopharmaceutical Sciences, Thailand. Suthipol Udompunturak MSc served as a statistical consultant for this study.	N = 40	Mean age is 44.66 years; 0 males, 40 females.	Mirtazapine 15mg (N = 13) vs. Mirtazapine 30mg (N = 14) vs. Placebo (N = 13).	13-weeks of treatment with 6 visits. Followed up at week: 1, 3, 5, 9, and 13.	Using PVAS scoring, reduction from baseline was observed in all groups. Mirtazapine 30mg had greatest improvement (65.46 vs 35.38; $p < 0.005$). Mirtazapine 15mg (68.79 vs 43.13; $p < 0.01$). Placebo (60.00 vs 42.00; $p < 0.05$). Mirtazapine 15 mg and 30 mg showed score reductions in PVAS were higher than placebo but were not significant ($p > 0.1$)	"Mirtazapine monotherapy at bedtime exhibited within-group significant improvement in most of the primary and secondary outcome variables, such as pain, sleep dysfunction, and FIQ in patients with FMS."	Small sample. Data suggests Mirtazapine taken at bedtime showed improvement in pain, sleep dysfunction, and FIQ in FM patients. However, depression was not improved.

Evidence for Serotonin Receptor Antagonists

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Späth 2004 (4.5)	5-Hydrotryptophan	RCT	Supported by Novartis Pharma GmbH, Nuremberg, Germany. Author Färber is an employee of Novartis Pharma GmbH.	N = 21 who met the American College of Rheumatology criteria for fibromyalgia	21 female, 0 male. Mean age tropisetron 51.2±11.7 years, placebo 48.5±8.7 years	Five daily intravenous bolus injections of 5mg tropisetron (N = 9) vs placebo injections (N = 12)	8 days	Graphic data indicate pain scores significantly lower in tropisetron group (p = 0.038) while VAS pain scores nearly significant (70 to 41.1 vs. from 64.4 to 57.7, p = 0.063). Baseline data suggest time since diagnosed favored placebo (2.9±5.3 vs. 0.4±0.7 years, labeled not significant)	"5-HT receptor antagonists provide significant pain relief for a group of FM patients."	Small sample size in both groups. Data suggest possible benefit of tropisetron in fibromyalgia patients.
Färber 2000 (4.0)	5-Hydrotryptophan	RCT	No mention of COI or sponsorship.	N = 403 who met the American College of Rheumatology criteria for fibromyalgia	373 female, 30 male. Mean age placebo group 48.5±8.4 years, tropisetron 5 mg 50.0±8.2, 10 mg	Daily treatment of one-time dosage for 10 days: placebo (N = 103) vs tropisetron 5 mg (N = 102) vs tropisetron 10 (N = 100)	10 days	Group percentage that achieved ≥ 35% pain score reduction from baseline to end of treatment: placebo 26.2%, tropisetron 5	"This study demonstrates the efficacy of short-term treatment with 5 mg tropisetron once daily in primary fibromyalgia. Treatment was well tolerated and prolonged clinical	5 mg = 39.2%, 10 mg = 13.0%, placebo = 6.3% which approximated the 15 mg dose making the results confusing and the possibility

					48.7±9.1 mg, 15 mg 48.1±9.2	vs tropisetron 15 (N = 98)		mg 39.2%, 10 mg tropisetron 30.0%, 15 mg tropisetron 23.5%. Significant difference between percentages achieved in placebo versus 5 mg (P = 0.033)	benefits were seen."	of spurious results.
Färber 2001 (4.0)	5-Hydrotryptophan	RCT	No mention of COI or sponsorship.	N = 403 who met the American College of Rheumatology criteria for fibromyalgia	373 female, 30 male. Mean age placebo group 48.5±8.4 years, tropisetron 5 mg 50.0±8.2, 10 mg 48.7±9.1 mg, 15 mg 48.1±9.2	Daily treatment of one-time dosage for 10 days: placebo (N = 103) vs tropisetron 5 mg (N = 102) vs tropisetron 10 (N = 100) vs tropisetron 15 (N = 98)	10 days	Group percentage that achieved ≥ 35% pain score reduction from baseline to end of treatment: placebo 26.2%, tropisetron 5 mg 39.2%, 10 mg tropisetron 30.0%, 15 mg tropisetron 23.5%. Significant difference between percentages achieved in placebo versus 5 mg (P = 0.033)	"Short-term treatment of fibromyalgia patients with 5 mg tropisetron for 10 days proved to be efficacious and well tolerated."	Same as Färber 2000.

Stratz 2001 (4.0)	5-Hydrotryptophan	Prospective	No mention of COI or sponsorship.	N = 42 who met the American College of Rheumatology criteria for fibromyalgia	41 female, 1 male. Mean age of tropisetron group 51, IV tropisetron group 51.5	2 mg tropisetron IV daily (N = 18) vs 2 mg intravenous tropisetron for 5-days (N = 24)	24 hours, 5 days, and again at 2 months	Mean pain intensity via visual analog scale (0-100) in those receiving IV tropisetron scores: baseline 62.9, after 24 hours 40.5 (P ≤ 0.0004). Mean pain intensity via visual analog scale in those receiving IV tropisetron for 5-days: baseline 60.33, after 5-days 30.41 (P ≤ 0.00002)	"In conclusion, intravenous injection of 2 mg of the 5-hydroxytryptamine$_3$ receptor antagonist tropisetron once daily for 5 days produced a longer-lasting therapeutic effect on fibromyalgia symptoms than did peroral daily treatment with 5 mg of this drug."	Data suggest IV tropisetron is better than per oral for a sustained therapeutic effect on the symptoms of fibromyalgia.

Evidence for Bupropion, Trazodone, or Pramipexole

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Holman 2005 (6.0)	Pramipexole	RCT	No mention of sponsorship or COI.	N = 60 who fulfilled the 1990 American College of Rheumatology criteria for fibromyalgia	57 female, 3 male. Mean age placebo group 46 years, pramipexole group 51 years	Pramipexole - 0.25 mg/week increasing to 4.5 mg/week (N = 39) vs Placebo (N = 21)	14 weeks after initial treatment	Between-group difference at study ending (placebo vs. pramipexole): Multidimensional Health Assessment Questionnaires – Pain: -1.77 (P = 0.008), Fatigue: -1.56 (P = 0.021), Global Status: -2.35 (P = 0.002), Function: -0.84 (P =	"In a subset of patients with fibromyalgia, ~50% of whom required narcotic analgesia and/or were disabled, treatment with pramipexole improved scores on assessments of pain, fatigue, function, and	Data suggest at 14 weeks, pramipexole patients reported a 36% decrease in their VAS pain score compared to 9% in placebo group.

								0.041), Psychiatric: -0.51 (P = 0.44)	global status, and was safe and well-tolerated."	

Evidence for Anti-Psychotics

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
McIntyre 2014 (6.0)	Quetiapine	RCT	Supported by AstraZeneca. Dr. McIntyre has received consulting fees and honoraria from AstraZeneca, Pfizer, Lundbeck, Eli Lilly, and Bristol-Myers Squibb (less than 10,000 each). Dr. Kouassi's laboratory has received research contracts from AstraZeneca. Dr Gendron owns stock or stock options in AstraZeneca.	N = 120	116 females, 4 males. Mean age is 51 years old.	Quetiapine XR (N = 61) vs Placebo (N = 59)	8 weeks	The mean change in the HAM-D score from baseline was significantly greater in the quetiapine XR group than in the placebo group (-10.0 vs -5.8; P = 0.001). Secondary efficacy outcomes were significantly greater in the quetiapine XR group than in the placebo group (BPI total score of -2.1 vs -.3; P = 0.007). Patients in the quetiapine XR group achieved a larger response and remission in regards to depression as compared to the placebo group. (25.9% P = 0.002) and (18.0% P = 0.004).	"Quetiapine XR significantly improved symptoms of depression and pain in patients with MDD and fibromyalgia. The results suggest that quetiapine XR exerts both antidepressant and analgesic effects in patients with this dual diagnosis. The safety and tolerability profiles of quetiapine XR were consistent with the known profile of this agent in patients with MDD alone."	Huge dropout rate. Data suggest quetiapine XR is superior to placebo for treating depression, pain and QoL in FM patients.
Potvin 2012 (5.0)	Quetapine	RCT	Funded by AstraZeneca Pharmaceuticals. Dr Marchand is holder of funds from the Canadian Institute	N = 51	51 females, 0 males. Mean age is 49.55 years old.	Quetiapine (N = 25) vs. Placebo (N = 26)	12 weeks	At baseline there were no significant differences between groups. FIQ total mean change for quetiapine (QTP) was -5.2 (P = 0.041) and placebo (PLC) was -	"In a small group of polymediated FM patients (mostly without MDD), low-dose quetiapine produced significant benefits	Pilot study suggesting the addiction of quetiapine positively impacted sleep and mood in FM patients

			of Health Research and is a supported member of the Centre de Recherche Clinique E´ tienne-Le Bel du Centre Hospitalier Universitaire de Sherbrooke. Dr Potvin is holder of a Junior 1 researcher scholarship from the Fonds de Recherche en Sante´ du Que´bec and is supported by the Louis-H Lafontaine Foundation.					2.5 (P = 0.262) from baseline. HDRS score mean change for QTP = -2.0 (P = 0.065) for PLC = -0.3 (P = 0.664). HARS mean change score for QTP = -1.5 (P = 0.124) for PLC = -1.2 (P = 0.748).	on sleep, uncertain effects on FM symptoms and mood, but no effect on pain."	but no effect on pain.
Calandre 2013 (5.0)	Quetiapine	RCT	Partial funding provided by AstraZeneca, as an investigator-sponsored study. Dr. Rico-Villademoros has served as a freelance consultant for AstraZeneca Famaceutica Spain. The remaining authors do not declare any	N = 90	88 females, 2 males. Mean age is 50.15 years.	Quetiapine (N = 45) vs. Amitriptyline (N = 45)	Screening at baseline and weeks 4, 8, 12, and 16.	There were no significant differences between baseline data for the groups. Change in the FIQ total score between quetiapine and amitriptyline were 4.14 (80% CI -0.70 to 8.98) for m-ITT sample and 6.13 (80% CI1.97 to 10.29) for the ITT sample. No significant differences were found between quetiapine XR and amitriptyline.	"Results appear to indicate that quetiapine XR does not provide similar efficacy to amitriptyline and is poorly tolerated in patients with fibromyalgia."	Open label trial with high dropout rate for both groups. Data suggest Quetiapine XR not as effective as amitriptyline for treating FM patients.

			conflict of interest.							

Evidence for NMDA Receptor Antagonist

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Olivan-Blázquez 2014 (7.5)	Memantine	RCT	No COI. Supported by grant from the Ministry of Health of the Government of Spain	N = 63 diagnosed with fibromyalgia according to the 1990 American College of Rheumatology criteria	61 female, 2 male. Mean age memantine group 48.09 years, placebo group 47.62 years	Memantine 20 mg/day for six months (N = 31) vs Placebo (N = 32)	Months 1, 3 and 6	Pain Visual Analogue Scale mean scores at 6 months: Memantine 4.87, Placebo 1.45, t=5.68 (P = 0.001). Pain level mean ratings via sphygmomanometer at 6 months: Memantine 115.81, Placebo 89.68, t=4.16 (P = 0.001)	"Although additional studies with larger sample sizes and longer follow-up times are needed, this study provides preliminary evidence of the utility of memantine for the treatment of FM."	Data suggest memantine showed efficacy over placebo for pain ratings as well as pain measured by sphygmomanometer at 6 months.
Fayed 2014 (5.0)	Memantine	RCT	No COI. Supported by Carlos III Institute of Health, Spanish Ministry of Health.	N = 25 diagnosed with fibromyalgia	23 female, 2 male. Mean age for memantine group 48.1 years, placebo group 48.5 years	Memantine 20 mg/day (N = 13) vs Placebo (N = 12)	6 months	Mean score differences within groups for memantine and placebo groups, respectively: CGI (illness severity) -0.5 (P = 0.2), 0.6 (P = 0.14). PAIN via sphygmomanometer 16.1 (P = 0.08), -30.7 (P = 0.04). PVAS (perceived pain via visual analog scale) -1.9 (P = 0.06), 1.2 (P = 0.09)	"Memantine treatment resulted in an increase in cerebral metabolism in FM patients, suggesting its utility for the treatment of the illness."	Small sample size. Data suggest memantine increased cerebral metabolism in fibromyalgia patients which may aid in treating fibromyalgia.

Evidence for Anti-Convulsants

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Crofford 2005 (7.5)	Pregabalin	RCT	Supported by Pfizer Global Research and Development. Author Crofford received consulting fees from Cypress Bioscience, Eli Lilly & Co., Orphan Pharmaceuticals, Pfizer, and Wyeth.	N = 529 with FM	484 female, 45 male. Mean age for placebo group 49.7 years, pregabalin 150 mg/day 48.0 years, pregabalin 300 mg/day 47.7 years, pregabalin 450 mg/day 48.9 years	Pregabalin 150 mg/day (N = 132) vs 300 mg/day (N = 134) vs 450 mg/day (N = 132) vs placebo (N = 131)	8 weeks	Pain ratings 7.0 baseline, reduced to 5.9/5.7/5.5/4.9 endpoint across increasing doses of medications (p <0.001 for 450mg vs. placebo). Percent with at least 50% improvements 28.9% in 450mg group (p = 0.003), but NS in other groups (18.9% vs. 13.0% vs. placebo 13.2%). Dropouts (22.5%) due to lack of efficacy greater in placebo (14%) vs. with increasing doses (9%/4%/6%). Adverse effects greater on medications and prompted dropouts in 13% of 450mg group vs. 7-8% in other groups and placebo (8%). Dizziness most common and dose related	"Pregabalin at 450 mg/day was efficacious for the treatment of FMS, reducing symptoms of pain, disturbed sleep, and fatigue compared with placebo. Pregabalin was well tolerated and improved global measures and quality of life."	Apparent dose-response benefit for sleep quality (graphic representation). Long-term efficacy is unclear.

								(placebo 10.7% vs. 22.7/31.3/49.2); somnolence next most common (4.6% vs. 15.9/27.6/28.0).		
Roth 2012 (6.0)	Pregabalin	RCT crossover	Supported by Pfizer Inc. Pfizer Inc. involved in study design and data analyses. Authors Bhadra, Whalen, and Resnick own stock or stock options in Pfizer.	N = 119 diagnosed with fibromyalgia according to American College of Rheumatology (1990 criteria) with history of disturbed sleep	103 female, 16 male. Mean age 48.4 years	First received pregabalin with target dosage being 300–450 mg/day (N = 59) vs First received placebo with same target dosage (N = 60)	4 weeks	Reduced polysomnographic (PSG) determined wake after sleep onset (WASO) in pregabalin treated (Week 4 difference = -19.2, P < 0.0001). Reduced pain score in pregabalin treated (Week 4 difference = -0.52, P = 0.0084).	"Patients with fibromyalgia treated with pregabalin had statistically significant and meaningful improvements in sleep, as assessed by PSG. Patients with fibromyalgia also reported decreased daily pain. Pregabalin was well tolerated."	Cross over design. Data suggest pregabalin patients had statistically significant improvement in sleep and had decreased pain.
Ohta 2012 (6.0)	Pregabalin	RCT	Supported by Pfizer Japan, Inc. Ohta, Ohkura, and Suzuki are employees of Pfizer Japan, Inc. Nishioka and Oka received consultancy fees from Pfizer Japan, Inc. for study participation.	N = 498 diagnosed with fibromyalgia according to the American College of Rheumatology 1990 criteria	443 female, 55 male. Mean age pregabalin group 47.9 years, placebo group 46.7 years	Pregabalin group - 150 mg/day to start, increasing to maintenance dose of 300 or 450 mg/day (N = 250) vs Placebo (N = 248)	15 weeks after initial treatment	Fibromyalgia Impact Questionnaire placebo-adjusted LS mean change from baseline with pregabalin: morning tiredness -0.59 (P = 0.0023), feeling good -0.63 (P = 0.0052), fatigue -0.49 (P = 0.0075), pain -0.47 (P = 0.0238), physical functioning -0.28	"This trial demonstrated that pregabalin, at doses of up to 450 mg/day, was effective for the symptomatic relief of pain in Japanese patients with fibromyalgia. Pregabalin also improved measures of	Data suggest pregabalin significantly reduced pain in Japanese FM patients as well as improved sleep and general function.

								(p=0.0376), housework -0.31 (P = 0.0729), anxiety -0.28 (P = 0.1011), stiffness -0.14 (P = 0.2568), depression (P = 0.4165), missing work -0.01 (P = 4768), total FIQ score -3.33 (P = 0.0144)	sleep and functioning and was well tolerated. These data indicate that pregabalin is an effective treatment option for the relief of pain and sleep problems in Japanese patients with fibromyalgia."	
Ramzy 2015 (6.0)	Pregabalin	RCT	No mention of COI. No sponsorship.	N = 75 diagnosed with fibromyalgia according to the standard 2010 criteria of the American College of Rheumatology	75 female, 0 male. Mean age amitriptyline 56.9±6.82 years, venlafaxine group 44.0±6.30 years, paroxetine 46.2±7.60 years	Oral amitriptyline - 25 mg/day (N = 24) vs venlafaxine - 75 mg/day (N = 25) vs paroxetine - 25 mg/ Day (N = 26), all patients also received 75 mg/day of pregabalin	Months 2, 4, and 6	Paroxetine and pregabalin group showed significantly lower Somatic Symptoms Scale-8 scores and Center for Epidemiological Studies Depression Scale scores from 18 (P < 0.05) and 10 weeks (P < 0.001), higher medication tolerability (P < 0.001), improved life satisfaction, mood, and sleep quality at most observation times (P < 0.05), fewer instances of dry mouth and elevated blood	"The combined use of pregabalin plus paroxetine offers an effective method with increased tolerability to reduce the somatic and depressive symptoms of fibromyalgia and to enhance the quality of life in affected individuals."	Data suggest pregabalin combined with paroxetine enhances quality of life and decreases depression in fibromyalgia patients.

								pressure (P < 0.02)		
Arnold 2015 (5.5)	Pregabalin	RCT crossover	Sponsored by Pfizer Inc. Author Arnold received consultancy and speaking fees from Pfizer Inc. Author Sarzi-Puttini received consulting fees, speaking fees, and/or honoraria from Pfizer Inc. Author Arsenault received research funding from and/or participated in a speakers' bureau for Pfizer Inc. Author Driscoll was an employee of inVentiv Health Clinical, a paid contractor to Pfizer Inc. Authors Khan, Brown, Clair, Scavone, Driscoll, Landen, and Pauer are fulltime employees of Pfizer	N = 193 diagnosed with fibromyalgia according to the 1990 American College of Rheumatology criteria for FM3, with a pain score of ≥ 4 on an 11-point numerical rating scale	180 female, 13 male. Mean age 50.1 years	Pregabalin dosage, starting at 150 mg/day and ending with dosage between 300 mg/day or 450 mg/day (N =) vs Placebo (N =), each group received medication for 6 weeks and then received other treatment for same time after a 2 week washout period	6 weeks after initial treatment	Mean pain scores significantly reduced with pregabalin (least squares mean difference from placebo= -0.61, 95% CI (-0.91, -0.31), (P = 0.0001). Pregabalin usage showed significantly improved Hospital Anxiety and Depression Scale scores for anxiety (difference = -0.95, P < 0.0001) and depression (difference = -0.88, P = 0.0005), Fibromyalgia Impact Questionnaire total score (difference = -6.60, P < 0.0001), sleep quality (difference = 0.57, P < 0.0001)	"Compared with placebo, pregabalin statistically significantly improved FM pain and other symptoms in patients taking antidepressant medication for comorbid depression."	Data suggest pregabalin affective in reducing pain in fibromyalgia patients taking antidepressants.

			Inc. with stock options with the company.							
Gilron 2016 (5.5)	Pregabalin	RCT crossover	Supported by grants from the Canadian Institutes of Health and CIHR-Pfizer Fx&D Collaborative Research Investigator Program. Gilron received support from Adynxx, Taris Biomedical, Astra Zeneca, Pfizer, and Johnson & Johnson and has received grants from the Canadian Institutes of Health Research, Physicians' Services Incorporated Foundation, and Queen's University.	N = 41 diagnosed with fibromyalgia according to the 1990 American College of Rheumatology criteria	36 female, 5 male. Median age 56 years (range 20-71)	Pregabalin group with target daily dosage of 450 mg (N = 41) vs duloxetine group with target daily dosage of 120 mg (N = 41) vs combination of pregabalin and dulexotine (N = 41) vs placebo (N = 41). Each participant received all four treatments with each treatment period being 6 weeks long	6 weeks after initial treatment	Of 41 participants randomized, 39 completed ≥2 treatments. Daily pain for placebo, pregabalin, duloxetine, and combination periods were 5.1, 5.0, 4.1, and 3.7, respectively (P < 0.05 for combination vs placebo, and pregabalin).	"Combining pregabalin and duloxetine for fibromyalgia improves multiple clinical outcomes vs monotherapy. Continued research should compare this and other combinations to monotherapy for fibromyalgia."	Data suggest the combination therapy (pregabalin and duloxetine) is superior to monotherapy.
Pauer 2011 (4.5)	Pregabalin	RCT	Supported by Pfizer Inc. Author Pauer is an employee of the Pfizer Global Research and	N = 736 diagnosed with fibromyalgia according to the 1990 American College of	673 female, 63 male. Mean age 48.5 years	Pregabalin dosage 300 mg/day (N = 184) vs pregabalin dosage 450 mg/day (N = 182) vs	12 weeks	Mean pain score differences from baseline for placebo, pregabalin 300 mg/day, 450 mg/day, 600 mg/day,	"Pregabalin demonstrated modest efficacy in pain, global assessment, and function in FM at 450	Data suggest some improvement in pain and global assessment. All doses of pregabalin improved sleep

			Development department.	Rheumatology criteria, had at least moderate pain (average pain score ≥ 4 on an 11-point numeric rating scale), and score ≥ 40 mm on the 100-mm pain visual analog scale of Short-Form McGill Pain Questionnaire		pregabalin dosage 600 mg/day (N = 186) vs placebo (N = 184)		respectively: -0.73, -1.06, -1.29, -0.96. Treatment difference from placebo for pregabalin 300 mg/day, 450 mg/day, 600 mg/day, respectively: -0.33 (P = 0.1694), -0.56 (P = 0.0132), -0.23 (P = 0.2361)	mg/day, and improved sleep across all dose levels, but it did not provide consistent evidence of benefit at 300 and 600 mg/day in this study. Pregabalin was generally well tolerated for the treatment of FM."	but there was inconsistent evidence at 300 mg/day and 600 mg/day doses.
Mease, 2013 (n=4.5)	Fibromyalgia	RCT	Sponsored by Forest Laboratories, Inc. Conflict of interest:	N=364 patients with fibromyalgia	Mean age: 49.4 years; 33 males, 319 females.	Pregabalin: (n=178) vs Pregabalin and Milnacipran: (n=179)	4 and 12 weeks	Responders reported improvement for MLN+PGN at 46.4% compared to PGN only at 20.8% (p<.001). Patients with at least 30% pain improvement was higher in MLN+PGN group than in PGN alone (45.8%, 19.7% respectively). Mean improvement from randomization VAS pain score was significantly greater in	"In this exploratory, open-label study, adding milnacipran to pregabalin improved global status, pain, and other symptoms in patients with fibromyalgia with an incomplete response to pregabalin treatment."	Open label study suggesting the addition of milnacipran to pregabalin improved pain and overall global outcomes in FM patients who did not have a complete response pregabalin alone.

								MLN+PGN group (±SEM) -20.77 (±1.92); PGN -6.43 (±1.93); p<.001. Significant differences in groups was observed at 2 weeks (P<.001). Most common AE with milnacipran and pregabalin were nausea (12.5%), fatigue (10.3%), and constipation (9.8%).		
Puiu 2016 (4.0)	Pregabalin	RCT crossover	Supported by Pfizer. Author Napadow's work supported by NIH grants. Author Pauer owns stock or stock options in Pfizer. Author Clauw received consulting fees from Cerephex, Eli Lilly, Merck, Nuvo, Forest, Cypress Biosciences, Theravance Biopharma, Johnson & Johnson, Pierre Fabre, Wyeth, UCB, AstraZeneca,	N = 23 diagnosed with fibromyalgia according to the 1990 American College of Rheumatology criteria	23 female, 0 male. Mean age 38.6±12.2 years	Pregabalin group - dose-escalated to 450 mg/day (N = 23) vs placebo (N = 23)	2 weeks after initial treatment	Only 16 participants considered for voxel-based morphometry analysis. Trends of reduced pain but no significant difference in pregabalin (VAS P = 0.114; SF-MPQ P = 0.216) or placebo treatment (VAS P = 0.223; SFMPQ P = 0.101). 15 participants Included in connectivity analyses and showed no significant reductions	"Short-term PGB treatment altered brain structure and evoked-pain connectivity, and these decreases were associated with reduced clinical pain. We speculate that these fairly rapid changes in GMV may be related to brain neuroplasticity. It is unknown whether these effects are generalizable	Crossover study. Small sample. Data suggest pregabalin treated fibromyalgia patients had decreased pain likely due to altered brain structure and evoked-pain connectivity.

			Jazz, Abbott, Iroko, Pfizer and Tonix and grant support from Pfizer, Cerephex, Eli Lilly, Merck, Nuvo, Forest, and Cypress Biosciences. Author Harris received consulting fees and grant support from Pfizer.					in clinical pain with pregabalin (VAS P = 0.183; SF-MPQ P = 0.328) or placebo treatment (VAS P = 0.101; SF-MPQ P = 0.196)	to other chronic pain states."	
Arnold 2014 (4.0)	Pregabalin	RCT	Supported by Pfizer Inc. Author Arnold received research support from Eli Lilly and Company, Pfizer, Forest, Theravance, Takeda, AstraZeneca, and Tonix; served as a consultant for Pfizer, Daiichi Sankyo, Theravance, Purdue, and Shire; and participated on a speakers bureau for Pfizer.	N = 121 diagnosed with fibromyalgia according to the 1990 American College of Rheumatology criteria for fibromyalgia	110 female, 11 male. Mean age pregabalin CR group 50.3 years, placebo group 49.3 years	Pregabalin CR with daily target dosage of 330-496 mg/day (N = 63) vs Placebo (N = 58)	13 weeks after double-blind phase initial treatment	Kaplan–Meier estimates over survival analysis of time in days to loss of therapeutic (LTR). During double-blind treatment phase, time to LTR significantly longer for pregabalin CR (P = 0.0214). Hazard ratio for pregabalin CR versus placebo = 0.590 (P = 0.0239). Percentage meeting LTR criteria during double-blind phase was 54.0% for pregabalin CR	"Time to LTR was significantly longer with pregabalin CR versus placebo in fibromyalgia patients who initially showed improvement with pregabalin CR, indicating maintenance of response. Pregabalin CR was well tolerated in most patients. Generalizability may be limited by study duration	Data suggest time to loss of therapeutic response (LTR) was longer in pregabalin CR group.

								and 70.7% for placebo	and selective population."	
Roth 2012 (4.0)	Pregabalin	RCT crossover	Supported by Pfizer. Author Roth received research funding and has acted as consultant or served on the Speaker's bureau for pharmaceutical companies including Pfizer. Authors Bhadra-Brown, Pitman, and Resnick are employees of, and have stock options in, Pfizer.	N = 119 diagnosed with fibromyalgia according to the 1990 American College of Rheumatology criteria, with disturbed sleep with difficulty maintaining sleep ≥3 times/week for ≥1 month	103 female, 16 male. Mean age 48.4 years	Pregabalin (150 to 450 mg/d) (N = 119) or matching placebo dosage (N = 119). All participants underwent both treatments, with a dose adjustment (up to day 14 of given period) and treatment maintenance (to day 29 of given period) phase	1 month after initial treatment	Pregabalin group presented significantly decreased wake after sleep onset (least squares mean difference = 19.2 min, P<0.0001), long latency to persistent sleep (7.2min, P=0.0458), total sleep time (25.7 minutes, P<0.0001) and sleep efficiency (5.41%, P<0.0001).	"Pregabalin improved sleep parameters characteristic of disturbed sleep in FM, by preventing awakenings and increasing sleep bout duration. These effects are reflected in, and correlated with a decrease in "light sleep" (stage 1) and an increase in "deep sleep" (slow wave sleep)."	Data suggest pregabalin improved sleep duration and decreased awakenings.
Mease 2008 (4.0)	Pregabalin	RCT	Supported by Pfizer Inc. Author Mease received research grant support from Pfizer Inc., Cypress Bioscience, Forest Laboratories, Inc., Eli Lilly and Company, Allergan, Wyeth Pharmaceuticals, Jazz	N = 748 diagnosed with fibromyalgia according to the American College of Rheumatology criteria	706 female, 42 male. Mean age for placebo group 48.6 years, pregabalin 300 mg/day 50.1 years, pregabalin 450 mg/day 47.7 years, pregabalin 600 mg/day 48.7 years	Pregabalin 300 mg/day (N = 185) vs pregabalin 450 mg/day (N = 183) vs pregabalin 600 mg/day (N = 190) vs placebo (N = 190)	14 weeks	Mean pain score for placebo, pregabalin 300 mg/day, 450 mg/day, and 600 mg/day, respectively: 5.7 (-1.4 change), 5.26 (-1.84), 5.23 (-1.87), 5.04 (-2.06). Treatment difference compared to placebo: pregabalin 300 mg/day -0.43 (P =	"Pregabalin at 300, 450, and 600 mg/day was efficacious and safe for treatment of pain associated with FM. Pregabalin monotherapy provides clinically meaningful benefit to	Data suggest improvement in pain in all pregabalin group.

			Pharmaceuticals, and Fralex Therapeutics.					0.0449), 450 mg/day -0.47 (P = 0.0449), 600 mg/day -0.66 (P = 0.0070)	patients with FM."	

Evidence for Gabapentin

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Arnold 2007 RCT	8.0	N = 150 with FM	Patients titrated 300mg a day for 1 week at bedtime, then 300mg BID for 1 week, then 1,200mg/day for 2 weeks, then 600mg TID for 2 weeks, then 600mg BID, and 1,200mg QHS. If not tolerated, 2,400mg/day, dose reduced and mean dose 1,800mg/day.	Dropouts higher in gabapentin group vs. controls (24% vs. 17%, p = 0.42). Brief Pain Inventory average pain severity scores decreased (baseline/12 weeks): gabapentin (5.7±1.4/3.2±2.0) vs. placebo (6.0±1.5/ 4.6±2.6; p = 0.015). Adverse effects were greater for dizziness (25.3% vs. 9.3%), sedation (24.0% vs. 4.0%), light headedness (14.7% vs. 1.3%), and weight gain (8% vs. 0%).	"Gabapentin (1,200-2,400mg a day) is safe and efficacious for the treatment of pain and other symptoms associated with fibromyalgia."	Mean pain scores appear graphically to continue to widen between active treatment and placebo over 12 week treatment duration. Long-term efficacy is unclear.
Crofford 2005 RCT	7.5	N = 529 with FM (91.5% females)	Pregabalin (150mg a day vs. 300mg vs. 450mg) vs. placebo.	Pain ratings 7.0 baseline, reduced to 5.9/5.7/5.5/4.9 endpoint across increasing doses of medications (p <0.001 for 450mg vs. placebo). Percent with at least 50% improvements 28.9% in 450mg group (p = 0.003), but NS in other groups (18.9% vs. 13.0% vs. placebo 13.2%). Dropouts (22.5%) due to lack of efficacy greater in placebo (14%) vs. with increasing doses (9%/4%/6%). Adverse effects	"Pregabalin at 450 mg/day was efficacious for the treatment of FMS, reducing symptoms of pain, disturbed sleep, and fatigue compared with placebo. Pregabalin was well tolerated and improved global measures and quality of life."	Apparent dose-response benefit for sleep quality (graphic representation). Long-term efficacy is unclear.

				greater on medications and prompted dropouts in 13% of 450mg group vs. 7-8% in other groups and placebo (8%). Dizziness most common and dose related (placebo 10.7% vs. 22.7/31.3/49.2); somnolence next most common (4.6% vs. 15.9/27.6/28.0).		

Evidence for Dehydroepiandrosterone (DHEA)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Finckh A 2005 (7.5)	Fibromyalgia	RCT	Supported by a research grant from the Rheumatology Department, CHUV. Dr. Finckh is supported by a scholarship from the Swiss National Science Foundation, the Geneva University Hospital, the Kirkland fellowship and NIH P60 AR 47782.	N= 52 postmenopausal women with FM	Mean age: 58.9 years;	Group 1 (n=26) was assigned DHEA (Dehydroepiandrosterone) treatment Vs. Group 2 (n=26)	At baseline, at 3 months, after the washout phase at 4 months, and at 8 months.	After 3 months of treatment with 50 mg of DHEA, median DHEA sulfate blood levels had tripled, but there was no improvement in well-being, pain, fatigue, cognitive dysfunction, functional impairment, depression, or anxiety, nor in objective measurements made by physicians. Androgenic side effects (greasy skin,	"DHEA does not improve quality of life, pain, fatigue, cognitive function, mood, or functional impairment in FM."	Crossover study. Data suggest lack of efficacy between DHEA and placebo for quality of life, pain, fatigue, cognitive function, mood or functional impairment from FM.

								acne, and increased growth of body hair) were more common during the DHEA treatment period (p = 0.02).		

Evidence for Calcitonin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Bessette L 1998 (4.5)	Fibromyalgia	RCT	This study was supported in part by NIH Grant no AR36308	N=11 patients fulfilling the American college of rheumatology classification criteria for fibromyalgia	Mean age: 43.7 years, 10 females, 1 male.	Participants alternatively received salmon calcitonin (100 IU sc) vs. Isotonic saline (1 cc sc) for four weeks, with a four weeks wash-out period between the treatments.	At week 0,2,4,8,10 and at week 12	None of the 11 outcomes measures (seven analog scales, dolorimetry score, and three SIP scores) showed a significant improvement with sCT. The principal side effect observed with sCT was nausea in ten patients and erythema in four patients.	"In summary, this study showed no evidence that sc sCT is effective in the treatment of fibromyalgia as none of the 11 end-point measured significantly improved. However, further research should continue to explore the relationship between serotonin abnormalities and fibromyalgia and evaluate other forms of serotonin precursors in this condition."	Crossover trial. Data suggest each of efficacy.

Evidence for Vitamin D

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Wepner F 2014 (4.5)	Fibromyalgia	RCT	No COI. This study was funded by Oesterreichische National bank	N=30 patients with FM	The mean age of the patients was 48.37 years; 27 women, 3 men	Treatment group (TG) vs. control group (CG). To achieve serum calcifediol levels (Vit D) between 32 and 48 ng/mL for 20 weeks via oral supplementation with cholecalciferol	At week 0, 1, 5, 13, 25 and week 49	Mean initial VAS score of all participants: 65.2 (±17.3), median 70. Treatment group had consistent improved VAS score. Both groups experienced increases at week 25. 2 (groups) x 4 (time points) variance analysis – significant (P = .025) group effect. Values for groups were similar at this time point, not Significantly different (P = .999)	"Optimization of calcifediol levels in FMS had a positive effect on the perception of pain. This economical therapy with a low side effect profile may well be considered in patients with FMS. However, further studies with larger patient numbers are needed to prove the hypothesis."	Data suggest vitamin D via oral supplementation may be beneficial for reducing pain in FM patients.

Evidence for Melatonin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
De Zanette 2014 (7.5)	Melatonin	RCT	This research was supported by grants and material support from the following Brazilian agencies: Committee for the Development of Higher Education Personnel – CAPES - PNPD/CAPES (grants to Rafael Vercelino; Deitos A; I.C.C. de Souza; (G. Laste	N = 63	63 females, 0 males. Mean age is 48.97 years.	Amitriptyline (N = 21) Vs Melatonin (N = 21) vs. Amitriptyline + Melatonin (N = 21)	6-weeks	FIQ score mean difference: for Amitriptyline = -12.19, Melatonin = -17.73, amitriptyline + melatonin = -24.65 (p = 0.04). Mean PPT mean difference: for amitriptyline = 0.2, melatonin = 0.4, amitriptyline + melatonin =0.54 (P = 0.03). Analgesic	"Melatonin alone or associated with amitriptyline was better than amitriptyline alone in improving pain on the VAS, FIQ and PPT, whereas its association with amitriptyline	Data suggest melatonin alone or in combination with amitriptyline significantly reduced pain (via VAS) compared to amitriptyline alone.

			MEC/MCTI/CAPES/CNPq/FAPs No 71/2013); J.R. Rozisky International Cooperation Program – CAPES (023/11) and material support; National Council for Scientific and Technological Development - CNPq (grants to Dr. I.L.S. Torres, Dr. W. Caumo); Postgraduate Program in Medical Sciences at the School of Medicine of the Federal University of Rio Grande do Sul (material support); Postgraduate Research Group at the Hospital de Clínicas de Porto Alegre (material support); Foundation for Support of Research at Rio Grande do Sul (FAPERGS) (grant to Schwertner A). No mention of COI.					doses mean difference: for amitriptyline = -0.72, melatonin = -0.79, amitriptyline + melatonin = -0.35 (P = 0.98). Number of tender points mean difference: amitriptyline = -3.45, melatonin = -3.75, amitriptyline + melatonin = -4.18 (P = 0.89). Pittsburg Sleep Questionnaire mean difference: amitriptyline = -7.47, melatonin = -6.42, amitriptyline + melatonin = -7.58 (P = 0.94).	produced only marginal additional clinical effects."	

Evidence for Hormone Replacement Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Stening, KD 2010 (4.5)	Hormone replacement Therapy (HRT)	RCT	Sponsored by the Swedish Research Council—Medicine (#7879), the Swedish Brain Foundation, the Health	N = 29	The mean age of the oestradiol-treatment group is 54 years. 0 males, 15 females. The mean age of the	Oestradiol-Treatment (N = 15) – Patients received transdermal 17β-oestradiol (50 µg/day). vs Placebo (N = 11) – Patients	Before treatment, after 8 weeks of treatment, and 20 weeks after termination of treatment.	No statistically significant differences were seen between treatment groups at any time point. The mean (S.D) data points that are of significance are reported in the 20 weeks after	"Compared with a placebo, 8 weeks of transdermal oestradiol treatment does not influence pain thresholds, pain tolerance or the experience of overall bodily pain	Data suggest 8 weeks of hormone replacement therapy pain in post-menopausal fibromyalgia women.

			Research Council in the South-East of Sweden and the Linneus University, Kalmar, Sweden. Mats Hammer receives remuneration for being on a scientific advisory board at Novo Nordisk, Denmark. Karl G. Henriksson has received honoraria for lectures on FM from Pierre-Fabre, Toulouse, France; Astra-Zeneca, Sodertalje, Sweden; and Pfizer, Sollentuna, Sweden. All other authors have declared no conflicts of interest.		placebo group is 54.9 years. 0 males, 11 females.	received a placebo treatment.		termination of treatment category for the following conditions: temperature threshold (°C) Placebo – 4.4 (2.4), p<0.05. Cold Pain Threshold (°C) Oestradiol – 17.5(6.4), p<0.01. Heat Pain Tolerance (°C) Placebo – 48(2.2), p<0.05). Pressure Pain threshold gluteal region, kPa Oestradiol - 244 (96), p<0.01. Cold pressor test, s Placebo- 20 (10), p<0.01. Cold pressor test (VAS) Oestradiol - 83 (13), p<0.01	in post-menopausal women suffering from FM."	

Evidence for Oxytocin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Mameli 2014 (4.0)	Oxytocin Nasal Spray	Randomized Crossover trial	No sponsorship or COI.	N = 14 women with fibromyalgia	Mean age: 51.9±7.8 Sex(M:F) 0:14	All patients received 3 weeks of daily intranasal oxytocin and 3 weeks of daily intranasal placebo.	9 weeks	There were no significant positive therapeutic effects of intranasal oxytocin.	"Unlikely, oxytocin nasal spray (80IU a day) did not induce positive therapeutic effects but resulted to be safe, devoid of toxicity, and easy to handle."	Crossover study design. Sparse methods. Data suggest lack of efficacy.

Evidence for Growth Hormone

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Bennett, 1998 (score=7.0)	Fibromyalgia	RCT	No mention of COI. Sponsored by a research grant from Genentech, Inc., San Francisco.	N = 50 participants with fibromyalgia	Mean age: 47.2 years; 0 males, 50 females.	Growth hormone group (N =25) vs Control Group (N =25)	9 months	Significant improvement in fibromyalgia impact was observed for the GH group compared to the control group (p<.04) and the fibromyalgia trigger point score (p<.03). Control group failed to show significant improvement at follow-up. Fifteen subjects in GH group and 6 in the control group showed global improvement (p<.02). No adverse effects were encountered.	"Women with fibromyalgia and low IGF-1 levels experienced an improvement in their overall symptomatology and number of tender points after 9 months of daily growth hormone therapy. This suggests that a secondary growth hormone deficiency may be responsible for some of the symptoms	Data suggest GH decreased numbers of tender points and overall symptoms of FM at 9 months and when GH was discontinued, symptoms worsened.

									of fibromyalgia."	
Cuatrecasas, 2007 (score=5.0)	Fibromyalgia	RCT	No COI and sponsored by Serono-Iberia (Merk España S.L)	N=24 patients with fibromyalgia for 1 year or more.	Mean age: 48.5 years; 0 males, 24 females.	GH group: (n=12) received .0125 mg/kg/d of GH with standard therapy Vs Control group: (n=12) received standard therapy only	3, 6, and 12 months	Reduction in number of tender points was observed in GH group compared to control group (p=.0001). Control group did not show statistical improvement, but GH group showed significant improvement in number of tender points (p=.001). Improvement in pain and fatigue FIQ subscales showed significance only for GH group (p<.05) as well as EQ-VAS scale (p<.001).	"The present findings indicate the advantage of adding a daily GH dose to the standard therapy in a subset of severe fibromyalgia patients with low IGF-1 serum levels."	Open label trial. Data suggest GH therapy in a particular subset of FM patients may reduce the number of tender points and improve overall FIQ scores.

Evidence of Pyridostigmine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Jones, 2008 (5.0)	Pyridostigmine and Exercise	RCT	Supported by the National Institute of Nursing Research Grant. COI, Dr. Jones has received fees (less than $10,000) for service on the	N = 165 patients with Fibromyalgia	Mean age 49.45±8.05 Sex(M:F) 5:160	Placebo group with Diet recall but No exercise were asked to complete a monthly log of food intake. (N = 41) Vs Placebo group, Group Exercise completed 60min group exercise classes 3x a week for 6 months.	6 months	Interaction of PYD and training exercise (F[1,143] = 0.04, (P = 0.849)), main effect of PYD (F [1,143] = 0.97, (P = 0.325)), and main effect of exercise (F [1,143] = 2.39, (P = 0.124)) all failed to reach significance.	"Neither the combination of PYD plus supervised exercise nor either treatment alone yielded improvement in most FM symptoms."	Data suggest that although PYD improved anxiety, sleep, exercise frequency (which improved fatigue and fitness), PYD alone or in combination with exercise did not

			Speaker's Bureau for Pfizer. Dr. Bennett has received speaking fees (less than $10,000 each) from Eli Lilly, Pfizer, and Gru¨nenthal.			(N = 39). Pyridostigmine (PYD(, with Diet recall but No group exercise (N=42) received PYD Bromide (180mg/day) for 6 months and asked to keep a monthly log of food intake Vs. Pyridostigminewith Group exercise received PYD bromide (180mg/day) for 6months and completed 60min group exercise classes 3x a week for 6 months. (N=43)				improve most FM associated symptoms.
Jones 2007 (4.0)	Pyridostigmine and Exercise	RCT	No mention of sponsorship or COI.	N = 165 patients with Fibromyalgia	Mean age 49.45±8.05 Sex(M:F) 5:160	Placebo group with Diet recall but No exercise were asked to complete a monthly log of food intake. (N = 41) vs Placebo group, Group Exercise completed 60min group exercise classes 3x a week for 6 months. (N = 39). Pyridostigmine (PYD(, with Diet recall but No group exercise (N=42) received PYD	6 months	PYD did not significantly increase Insulin Like Growth Factor-I (IGF-I) during exercise classes. Interaction of PYD and exercise classes for IGF-I (F (1,147) = 0.02, (p = 0.891)).	"A combination of triweekly supervised exercise plus the daily use of PYD for 6 months failed to increased IGF-I levels in patients with FM, despite the confirmation that PYD normalizes the acute GH response to strenuous aerobic exercise."	High dropout rate. Data suggest lack of efficacy.

						Bromide (180mg/day) for 6 months and asked to keep a monthly log of food intake Vs. Pyridostigminewith Group exercise received PYD bromide (180mg/day) for 6months and completed 60min group exercise classes 3x a week for 6 months. (N=43				

Evidence for Ritanserin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Olin, 1998 (4.0)	Ritanserin	RCT	No mention of sponsorship. COI, Reinhild Klein is supported by the Deutsche Forschungsgemeinschaft, Bonn-Bad Godesberg.	N = 51 patients with Fibromyalgia	Mean age: 44 Sex(M:F) 0:51	Ritanserin group (N=24) received 10mg of ritanserin daily for 16 weeks. Placebo group (N=27) received placebo treatment.	16 weeks	No significant differences were found between the ritanserin group and placebo group in pain, fatigue, sleeping, morning stiffness, IBS, anxiety, physical performance or consumption of analgesics. Incidence and activity of antibodies were not affected by ritanserin or placebo.	"Although the results of this therapeutic trial may be disappointing in not supporting a traditional theory, they again underline the difficulties of finding a therapeutic regimen that can ameliorate efficiently the plethora of FM-Associated symptoms."	Data suggest Ritanserin had little effect on FM patients and there was no difference in pain, fatigue, sleep, morning stiffness, anxiety or tender points.

Evidence for S-Adenosylmethionine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Volkmann, 1997 (Score=8.0)	S-Adenosylmethionine	RCT	Supported by ASTA Medica AG, Weismullerstrasse 15, Frankfurt am Main, Germany. No mention of COI.	N = 34 with Fibromyalgia	Mean age: 49 years; Gender not specified.	(SAMe) (n=34) – Patients received 600 mg of Intravenous S-adenosyl-L-Methionine daily for 10 days. vs. Placebo (n=34) – patients received the placebo for 10 days daily. Treatment periods daily for 6 days, then 1 day off and another 4 days of treatments.	No follow up.	Pain at rest decreased from 65/100 to 56 for SAMe while change was 65 to 69 on placebo (p = 0.08).	"Study only showed statistically non-significant trends towards a beneficial effect of i.v. SAMe in FM with regard to certain subjective symptoms. However, due to lack of statistical power and since the present findings were in line with previous results, we cannot discard the possibility of a moderate beneficial effect of SAMe in FM."	Four patients dropped out due to adverse effects of SAMe.
Tavoni, 1987 (Score=5.5)	S-Adenosylmethionine	RCT	No mention of sponsorship or COI.	N = 17 with Fibromyalgia	Mean age: 44.5 years; Gender not specified.	SAMe (n=17) – patients received intramuscular injections 200 mg of S-Adenosylmethionine daily for 21 days. vs. Placebo (n=17) – patients received intramuscular injections of the placebo daily for 21 weeks.	No follow up.	Number of trigger points plus painful anatomic sites decreased after administration of SAMe (p <0.02) but not after placebo treatment. Scores on Hamilton Depression Rating Scale and SAD rating scales	"This preliminary study confirms that close relationship between primary fibromyalgia and psychologic disturbances, particularly with regards to a depressive state. SAMe treatment, by improving the depressive state and reducing the number of trigger points, seems to be an effective and	Results not well reported, but graphically appear to indicate no significant differences between two groups. Study details not well defined.

								improved after SAMe administration (p <0.05 and p <0.005, respectively), did not significantly change after placebo treatment.	safe therapy in the management of primary fibromyalgia."	
Jacobson, 1991 (5.5)	S-Adenosylmethionine	RCT	No mention of sponsorship or COI.	N = 44 patients with Fibromyalgia	Mean age of Actively treated group 49.8, Placebo group 49.0 Sex(M:F) 6:38	Treatment group (N=22) received 800mg of S-Adenosylmethionine daily for 6 weeks. Placebo group (N = 22) received placebo medication for 6 weeks.	6 weeks	At 6 weeks, morning stiffness was significantly lower in treatment group vs placebo group (45 vs 60 (p=0.03)). Visual analog scales showed significant differences in frequency of resting pain during the past week (3.3 vs. 4.0 (p = 0.002)) & fatigue (3.7 vs 4.5 (p = 0.04)) in treatment group in comparison to placebo.	"S-adenosylmethionine has some beneficial effects on primary fibromyalgia and could be an important option in treatment relief."	Data suggest lack of efficacy.

Evidence for Creatine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Alves C 2013(5.5)	Fibromyalgia	RCT	Supported by CNPq and FAPESP (FBB: 2011/08302-0).	N= 28 women with fibromyalgia	Mean age: 48.2 years;	Placebo (n= 13) Vs. Creatine (n=15)	At baseline and after 16 weeks	After the intervention, the creatine group presented higher muscle phosphoryl creatine content when compared with the placebo group (+80.3% versus -2.7%; *P* = 0.04). Furthermore, the creatine group presented greater muscle strength than the placebo group in the leg press and chest press exercises (+9.8% and +1.2% for creatine versus -0.5% and -7.2% for placebo, respectively; *P* = 0.02 and *P* = 0.002, respectively). Isometric strength was greater in the creatine group than in the placebo group (+6.4% versus -3.2%; *P* = 0.007).	"To conclude, creatine supplementation increased intramuscular phosphorylcreatine content by 80% and improved lower- and upper-body muscle function, with minor effects in fibromyalgia general symptoms. Importantly, no side effects were noticed. Altogether, these findings reveal the potential of creatine supplementation as a useful dietary intervention to improve muscle function in patients with fibromyalgia"	Data suggest that at 16 weeks creatinine improved muscle function in FM patients.

Evidence for Terguride

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Distler, O 2009 (Score = 6)	Fibromyalgia	RCT	Sponsorship by ErgoNex Pharma. COI Dr. Distler has received consulting fees, speaking fees, and/or honoraria from ErgoNex Pharma (less than $10,000). Dr. Eich has received consulting fees, speaking fees, and/or honoraria from Pfizer and Eli Lilly (less than $10,000 each). Dr. Bendszus has received consulting fees, speaking fees, and/or honoraria from Cordis and	N = 99	88 females, 11 males; mean age 48.7	Terguride; .5 mg, 3-week titration period up to 6 tablets per day, 9 week fixed dose, 5 days down titration period. (N = 65) Vs Placebo (N = 34)	12 weeks	Pain VAS score (mean –1 mm [95% CI –12, 9]; (p = 0.795)), the FIQ score (–2.6 [95% CI –11.6, 6.5]; (p = 0.572), and the TPS (0.8 [95% CI –2.3, 0.3]; (p = 0.659)) from baseline to V12 (LOCF) ITT analysis, the differences in the mean decrease in pain intensity (-10 mm [95% CI -42, 2]; (p = 0.578), in the FIQ score (-16.7 [95% CI -30.1, 1.7]; (p = 0.093), and in the TPS (-10.9 [95% CI -23.8, 2.0]; (p = 0.087) from baseline to V12 (LOCF) Effects of terguride treatment on the FIQ score inpatients with cervical spine stenosis (mean -18.54 [95% CI -36.6, -0.45]; (p = 0.046) Terguride versus placebo treatment on the FIQ score (-2.18; (p = 0.0328), do work (-1.88; (p = 0.0917)), fatigue (-	Terguride treatment did not improve pain, the FIQ score, the TPS, or the HDS score in the total study population. However, a subgroup of patients with cervical spine stenosis seemed to benefit from terguride treatment.	Data suggest lack of efficacy.

			Micrus Endovascular (less than $10,000 each), and ErgoNex Pharma (more than $10,000). Dr. Reiter owns stock or stock options in ErgoNex Pharma. Dr. Muller-Ladner has received consulting fees from ErgoNex Pharma (less than $10,000).					1.57; (p = 0.2359)), rested (-1.48; (p = 0.3382)), stiffness (-1.67; (p = 0.1288)), anxiety (-3.66; (p = 0.0411)), and depression (-2.33; (p = 0.132))		

Evidence for Valcyclovir

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kendall, SA 2004 6	Valacyclovir	RCT	Sponsored by GlaxoSmithKline Pharma A/S, Denmark; The Oak Foundation; The Danish Health Foundation; and The Foundation of Lykfeldt. No mention of COI.	N = 60 patients with fibromyalgia.	The mean age of the Valacyclovir group is 48.9 years. 2 males, 28 females. The mean age of the placebo group is 50.2 years.	Valacyclovir (N = 30) – Patients received 1 tablet of Valacyclovir 3 times daily during a 6 week period vs Placebo (N = 30) – Patients received 1 tablet of placebo (lactose) 3 times	No follow up	The primary outcome is Pain assessed on the visual analog score (VAS). The pain VAS score in centimeters was 7.9 ± 1.7 and 7.0 ± 2.3 for Pre-Valacyclovir and Post-Valacyclovir, respectively. The pain VAS score in centimeters was 7.8	"Valacyclovir cannot be recommended as a therapy for FM at this point."	Data suggests lack of efficacy.

					0 males, 30 females.	daily during a 6 week period.		± 2.2 and 7.0 ± 2.3 for Pre-Placebo and Post-Placebo, respectively. P=0.45.		

Evidence for Sodium Oxybate

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Scharf 2002 (6.0)	Sodium Oxybate	RCT crossover	No mention of COI or sponsorship.	N = 24 with fibromyalgia	24 female, 0 male. Mean age 48.92 years	6 ml of 500 mg/ml sodium oxybate solution diluted in water to total 2 oz., 2 nightly dosages 4 hours apart (N = 24) vs placebo (N = 20)	4 week after initial treatment	Tender point index (TPI): significant decrease of 8.5 in sodium oxybate treatment compared to increase of 0.4 in placebo treatment (P = 0.0079). Three of four pain scores and three fatigue scores significantly improved in sodium oxybate treatment compared to placebo (P < 0.005)	"Sodium oxybate effectively reduced the symptoms of pain and fatigue in patients with FM, and dramatically reduced the sleep abnormalities (alpha intrusion and decreased slow-wave sleep) associated with the nonrestorative sleep characteristic of this disorder."	Crossover trial. Data suggest sodium oxybate reduced the symptoms of pain and fatigue and significantly reduced sleep abnormalities in fibromyalgia patients.
Russell 2009 (5.5)	Sodium Oxybate	RCT	Supported by Orphan Pharmaceuticals (owned subsidiary of Jazz Pharmaceuticals). Authors Russell, Perkins, and Michalek	N = 188 who met the 1990 American College of Rheumatology criteria for fibromyalgia	178 female, 10 male. Mean age placebo group 47.3±10.6 years, SO 4.5 gm	Oral solution of sodium oxybate (4.5 gm/night) in two doses 2.5-4 hours apart for 8 weeks (N =	8 weeks	Mean change from baseline in pain score via visual analog scale: placebo -8.6, 4.5 gm -16.2 (P=0.04 when compared to placebo), -15.9	"Sodium oxybate therapy was well tolerated and significantly improved the symptoms of	Data suggest sodium oxybate therapy improved symptoms of fibromyalgia.

			received research support from Jazz Pharmaceuticals.		47.4±12.1 years, SO 6 gm 45.5±11.6 years	58) vs sodium oxybate (6 gm/night) (N = 66) vs placebo (N = 64)		(P=0.03 when compared to placebo). Mean change from baseline in FIQ scores: placebo -10.4, 4.5 gm -20.4 (P=0.007 when compared to placebo), 6 gm -18.4 (P=0.02)	FMS. Further study of sodium oxybate as a novel therapeutic option for FMS is warranted."	
Russell 2011 (5.0)	Sodium Oxybate	RCT	Partially supported by The Curry Rockefeller Group for editorial and graphic assistance. No mention of COI.	N = 548 who met the 1990 American College of Rheumatology criteria for fibromyalgia, body mass index of <40 , ≥50 on a 100-mm Pain Visual Analog Scale	500 female, 48 male. Mean age for placebo group 46.5 year, SXB 4.5 g 47.0 years, SXB 6 g 47.5 years	Two oral solutions of sodium oxybate 4.5 g, 2.5-4 hours apart each night (N = 182) vs 6 g per night (N = 182) vs placebo (N = 183)	2 weeks after final treatment	Mean change in pain visual analog scale scores: placebo -17.8±2.2, sodium oxybate 4.5 g -28.8±2.1 (P < 0.001 when compared to placebo), sodium oxybate 6 g -31.6±2.1 (P < 0.001)	"These results expand the evidence from previous clinical trials suggesting that SXB is effective and safe in FM."	Data suggest both groups receiving SXB reported better or very much better global improvements and more than 50% improvement in pain.
Spaeth 2011 (5.0)	Sodium Oxybate	RCT	Supported by Jazz Pharmaceuticals, Inc. COI, one or more authors have received or will receive benefits for personal or professional use.	N = 573 who met the 1990 American College of Rheumatology criteria for fibromyalgia	513 female, 60 male. Mean age 46.6 years	Two oral solutions of sodium oxybate 4.5 g, 2.5-4 hours apart each night (N = 195) vs sodium oxybate 6 g (N = 190) vs placebo (N = 188)	14 weeks after initial treatment	Mean change in pain visual analog scale scores: placebo -11.9±2.0, sodium oxybate 4.5 g -19.2±2.0 (P = 0.010 when compared to placebo), sodium oxybate 6.0 g -23.4±1.9 (P < 0.001 when compared to placebo)	"These results, combined with findings from previous phase 2 and 3 studies, provide supportive evidence that SXB therapy affords important benefits across multiple symptoms in subjects with fibromyalgia."	Data suggest sodium oxybate improves fibromyalgia symptoms of pain and sleep.

Moldofsky 2010 (4.0)	Sodium Oxybate	RCT	Supported by Jazz Pharmaceuticals, Inc. COI, one or more of the authors have received or will receive benefits for personal or professional use.	N = 151 who met the 1990 American College of Rheumatology criteria for fibromyalgia	142 female, 9 male. Mean age 46.9 years	4.5 g sodium oxybate dosage per night (N = 51) vs 6 g per night (N = 46) vs placebo (N = 54)	8 weeks after initial treatment	Mean change in indicators of daytime functioning for placebo, sodium oxybate 4.5 g, and sodium oxybate 6 g, respectively - Functional outcome of sleep: 1.0, 2.6 (P = 0.27 when compared to placebo), 2.7 (P = 0.028 when compared to placebo). SF-36 Vitality domain: 5.5, 11.1 (P = 0.016 when compared to placebo), 12.8 (P = 0.003 when compared to placebo)	"This large cohort of patients with FM demonstrated that SXB treatment improved EEG sleep physiology and sleep-related FM symptoms."	Data suggest improvement from sodium oxybate treatment for fibromyalgia sleep physiology and sleep symptoms compared to placebo.

Evidence for Zolpidem

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Moldofsky, H 1996 (Score = 4.5)	Fibromyalgia	RCT	Sponsorship by a grant from Lorex Pharmaceuticals. No mention of COI.	N = 16 with Fibromyalgia and chronic fatigue.	No mention of sex; Mean age 42	Zolpidem dose (ZPD) (5, 10, 15 mg) N = 10 vs Placebo N = 6	16 days	Placebo vs ZPD 5 vs ZPD 10 vs ZPD 15. Sleep quality 3.1, 3.1, 2.7, 2.6 (p = 0.064). No. of awakenings 2.7, 2.3, 1.7, 2.0 (p = 0.008) Sleep Improvement 3.1, 3.0, 2.4, 2.4 (p = 0.27)	"Short term treatment with Zolpidem (5 to 15 mg0 does not affect the pain of FM but is useful for sleep and daytime energy in this patient population."	Data suggest short term use of Zolpidem improves sleep but does not improve pain.

								Time to fall asleep 3.0, 3.1, 3.5, 3.8 (p = 0.049)		

Evidence for Weight Reduction

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Senna 2012 (6.0)	Weight Reduction	RCT	No sponsorship or COI.	N = 83 obese patients who met the 1990 American College of Rheumatology criteria for fibromyalgia	75 female, 8 male. Mean age for control group 46.3±14.4 years, weight reduction group 44.8±13.6 years	Dietary weight loss group – 1,200 kcal/day for 6 months, instruction manuals with sample meal plans and recipes (N = 41) vs Control group – follow medical treatment given by physical, could not participate in weight reduction program (N = 42)	6 months	BMI significantly reduced after 6 months in the dietary weight loss group: 32.3±1.4 to 29.03±1.22 kg/m2 (p<0.001), no significant change in control group. BMI of weight loss group statistically lower than control group (p<0.001)	"Our results suggest that weight reduction should be a part of fibromyalgia treatment."	Data suggest weight loss in fibromyalgia patients led to improved outcomes in quality of life as well as depression, sleep quality, and numbers of tender points.

Evidence for Dietary Interventions

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ali 2009 (6.5)	Micronutrients (Myers' Cocktail)	RCT	No COI. Supported by grants from the National Center for Complementary and Alternative Medicine (NCCAM) at the National	N = 34 who met the American College of Rheumatology fibromyalgia criteria	33 female, 1 male. Mean age for micronutrient group 51.7 years, placebo group 50.7	Intravenously received Myer's cocktail (water-soluble vitamins and minerals) once a week for 8 weeks (N = 16) vs Placebo solution (N = 18)	Weeks 8 and 12	Mean scores at week 12 for the micronutrients group and placebo, respectively: Totally Survey Site Scores -17.1, -20.7 (p=0.39). Fibromyalgia Intensity Score -1.0, -1.1 (p=0.50)	"This first controlled pilot study established the safety and feasibility of treating FMS with IVMT. Most subjects experienced relief as	Pilot study. Data suggest lack of efficacy.

			Institutes of Health.						compared to baseline, but no statistically significant differences were seen between IVMT and placebo. The efficacy of IVMT for fibromyalgia, relative to placebo, is as yet uncertain."	
Slim 2016 (5.0)	Gluten-free diet	RCT	No sponsorship or COI.	N = 75 who met the 2010 American College of Rheumatology fibromyalgia criteria	73 female, 2 male. Median age for gluten-free diet group 52 years, hypocaloric diet group 53 years	Gluten-free diet (GFD), no caloric restriction, given supplementary material (N = 35) vs Hypocaloric diet (HCD), small meals divided into 5 portions each day, did not exceed 1500 kcal/d, given detailed dietary program	24 weeks	Linear Square mean change in gluten sensitivity symptoms count for GFD and HCD, respectively: -2.44±0.4, -2.13±0.37. Linear square mean difference GFD-HCD -0.314 (ANCOVA p = 0.343).	"Both dietary interventions were associated with similar beneficial outcomes in reducing gluten sensitivity symptoms and other secondary outcomes. However, despite its specificity, GFD was not superior to HCD in reducing the number of gluten sensitivity symptoms or secondary outcomes."	Pilot study. Data suggest comparable in efficacy in both groups. A gluten-free diet is not superior to a hypocaloric diet for reducing fibromyalgia symptoms.

Evidence for Acetyl 1-carnitine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Rossini M 2007 (5.0)	Fibromyalgia	RCT	No mention of COI or sponsorship	N= 89 patients with fibromyalgia	Mean age: 46.9 years	Placebo (N = 47) Vs. Acetyl L-carnitine or LAC (N = 42)	4 weeks after treatment	The "total myalgic score" and the number of positive tender points declined significantly and equally in both groups until the 6th week of treatment. At the 10th week both parameters remained unchanged in the placebo group but they continued to improve in the LAC group with a statistically significant between-group difference. Most VAS scores significantly improved in both groups. A statistically significant between-group difference was observed for depression and musculo-skeletal pain. Significantly larger improvements in SF36 questionnaire were observed in LAC than in placebo group for most parameters.	"Although this experience deserves further studies, these results indicate that LAC may be of benefit in patients with FMS, providing improvement in pain as well as the general and mental health of these patients."	High dropout rate. Data suggest acetyl-1-carnitine "may" provide pain relief to FM patients.

Evidence for Zopiclone

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Gronblad, 1993 (4.0)	Zopiclone	RCT	Supported by Rhone-Poulenc Rorer, Finland. No mention of COI.	N = 33 patients with fibromyalgia	Mean age: 45 Sex(M:F) 2:31	Zopiclone group (N=14) received 7.5mg of zopiclone daily for 8 weeks. The placebo group (N=19) received placebo medication for 8 weeks.	4 weeks and 8 weeks	Examiners assessed that half the patients in both groups showed improvement in their overall condition at week 8. 93% of the zopiclone group reported improvement in sleep scores at 4 weeks and 79% at 8 weeks. In comparison to placebo group where 64% reported improvement at weeks 4 & 8.	"In summary, zopiclone appears to have only marginal effects on several different measure of tenderness, pain, and discomfort."	Data suggest zopiclone group reported improvement in 80% of fibromyalgia patients 8 weeks post intervention. Other variables were similar between groups.
Drewes, 1991 (5.5)	Zopiclone	RCT	Supported by Rhone-Poulenc A/S. No mention of COI.	N = 45 patients with fibromyalgia.	Mean age: 50 Sex(M:F) 0:45	Zopiclone group (N=20) received 7.5mg of zopiclone a day for 12 weeks. Placebo group (N=21) received a placebo tablet daily for 12 weeks.	6 & 12 weeks	Zopiclone group showed significant improvement in overall evaluation of sleep in comparison to the placebo group. No significant differences were found between groups for pain or stiffness.	"Zopiclone seems to be of value in treating the sleep complaints in patients with fibromyalgia."	Data suggest zopiclone does not improve FM pain but may help with sleep disturbances. A placebo effect was observed.

Evidence for Dolasetron

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Vergne-Salle, P 2010 (Score = 6)	Fibromyalgia	RCT	Sponsorship by grant from the Clinical Research Program	N = 60 patients with FM	53 females, 7 males; mean age 50.2.	Dolasetron 12.5 mg/d (N = 29) vs	12 months	pain intensity at M3 Dolasetron-treated patients (p = 0.04, -21.3 compared with	"Intermittent IV Dolasetron was safe and efficacious for the reduction of pain	Data suggest Dolasetron may be beneficial for pain

			from French Ministry of Health. No mention of COI.			placebo (N = 31)		placebo controls (-5.9). patients in the Dolasetron group had P30% and P50% improvement in pain (42.5% and 28% respectively in the Dolasetron group vs 25% and 16% in the placebo group. The PGIC in the Dolasetron group at M3 (p = 0.02).	intensity associated with FM at 3 months."	reduction in FM patients.

Evidence for Skeletal Muscle Relaxants

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Moldofsky 2011 (4.0)	Cyclobenzaprine	RCT	Supported by TONIX Pharmaceuticals Inc., New York. Authors Harris and Lederman are employees of TONIX.	N = 36 with sleep disturbances and who met the American College of Rheumatology 2001 criteria for fibromyalgia	35 female, 1 male. Mean age VLD CBP group 45.9 years, placebo 39.3 years	very low dose cyclobenzaprine (VLD CBP), ≤ 4 mg/day for 8 weeks (N=18) vs placebo (N=18)	8 weeks after initial treatment	Mean changes in musculoskeletal pain for VLD CBP and placebo groups, respectively: -0.6, 0. T-test comparison within groups: VLD CPB (p=0.010), Placebo (p=1.000). VLD CPB compared to placebo ANOVA (p=.044)	"Bedtime VLD CBP treatment improved core FM symptoms. Nights with $CAP_{A2+A3(Norm)}$ ≤ 33% may provide a biomarker for assessing treatment effects on nonrestorative sleep and associated fatigue and mood symptoms in persons with FM.	Spares methods. Data suggest cyclobenzaprine taken at bedtime may improve sleep.

Evidence of Alpha1-Antitrypsin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Alegre 2012 (6.0)	Antitrypsin	RCT crossover	No mention of COI or sponsorship.	N = 13 who met the 1990 American College of Rheumatology criteria for fibromyalgia	12 female, 1 male. Mean age of AAT then placebo group 47.7 years, placebo then AAT group 47.2 years	First received intravenous human plasma-derived AAT (60 mg/kg body weight) (N = 7) vs first received placebo (equal volume of intravenous normal saline) (N = 6). Each treatment phase lasted 9 weeks	6 weeks after final treatment	Mean change for daily pain score via a visual analog scale: AAT to placebo group 0.07, placebo to AAT group -0.85. No statistical difference found between these scores or in any scores for secondary measurements	"Treatment with a human plasma-derived AAT concentrate did not demonstrate significant improvement over placebo on reducing pain severity and other symptoms of FM. Further research should examine other FM subpopulations and drug doses"	Crossover with small sample (pilot study). Data suggest no advantage for use of alpha 1-Antitrypsin in fibromyalgia (lack of efficacy).

Evidence for Opioids

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Russell, 2000 (Score=7.0)	Opiods	RCT	Sponsored by Ortho-McNeil Pharmaceutical, Raritan, New Jersey. No mention of COI.	N = 69 with Fibromyalgia	Mean age: 48.4 years; 4 males, 96 females.	All patients enter an open-label phase in which they received a dosage titirated up to 200 mg for 3 weeks. Patients could either dropout or enter the Double blind phase: Tramadol (n=35) – patients received 200 mg of Tramadol daily for 6 weeks. vs. Placebo (n=34) – patients received the placebo daily for 6 weeks.	No follow up.	Patients more likely to discontinue placebo than tramadol due to inadequate pain relief. Substantial proportion of tramadol group also discontinued treatment (42.9%) vs. 73% placebo. Pain intensity scale ratings favored tramadol (5.9±2.9 vs. 7.2±2.3, p = 0.045). FIQ scores not different (tramadol 44.6±18.0 vs. placebo 47.2±15.7). Tender point scores did not differ (p = 0.449).	"These results support the efficacy of tramadol over a period of 6 weeks in a double blind study for the treatment of pain of fibromyalgia in a group of patients who had been determined to tolerate it and perceive a benefit."	Thirty-one patients either did not tolerate or did not achieve benefit to continue to RCT from an open-label phase.
Bennett, 2003 (Score=7.0)	Opiods	RCT	Sponsored by Ortho- McNeil Pharmaceutical, Inc, Raritan, New	N = 315 with Fibromyalgia (ACR	Mean age: 50 years; 21 males, 294 females.	Tramadol/ acetaminophen (n=158) – patients received	No follow-up.	Dropouts 52% placebo vs. 38% medication, but high for both mostly lack of efficacy. FIQ total scores	"A tramadol/ acetaminophen combination tablet was effective for the	Long-term effects and safety are not able to be addressed with this short-term

			Jersey. No mention of COI.	criteria used)		combination tablets (37.5mg/325mg tablets respectively) daily for 91 days. vs. Placebo (n=157) patients received matching placebo 1-2 tablets QID for 91 days of treatment.		(baseline to final visit): tramadol/ acetaminophen (54±11 to 44±17) vs. placebo (55±11 to 50±15; p = 0.008). Final pain scores 18% lower in active treatment (p <0.001). Somewhat more nausea (p = 0.06), pruritus (p = 0.01), dizziness (p = 0.19), constipation (p = 0.04), somnolence (p = 0.17) in tramadol group.	treatment of fibromyalgia pain without any serious adverse effects."	study design. Large dropout rates limit strength of conclusions, particularly where final pain ratings in treatment group were not markedly lower.
Biasi, 1998 (Score=6.0)	Opiods	RCT	No mention of sponsorship or COI.	N = 12 with Fibromyalgia	Mean age: 46.1 years; 1 male, 11 females.	Tramadol (n=11) – Patients received Two injections of tramadol 100mg IV. vs. Placebo (n=11) - Patients received a placebo for single dose treatment. 1-week washout between treatments.	No follow up.	Graphic data show 1st administration of tramadol decreased VAS pain ratings from 56-42 while placebo increased from 42-51. At crossover, placebo group decreased from 56 to 49 while tramadol group decreased slightly from 43 to 40.	"From these results it appears that tramadol provided more marked pain relief during the first treatment cycle, assessed using the VAS. Tender point assessed on the basis of pressure measurements, a specific method for patients with fibromyalgia, showed no difference between the two treatment groups."	Study as conducted was invasive. One patient dropped after developing hypotension and another after nausea, tremors, epigastric pain, and dizziness 4 hours after treatment.

Evidence for Acupuncture

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Harte, S 2013 (Score = 8)	Fibromyalgia	RCT	Sponsorship by funding from; Department of Army Grants, National Institutes of health grants, brain and Immuno-Imaging Grant from the Dana Foundation. No mention of COI.	N = 50 patients with Fibromyalgia.	50 females; Mean age 46.0	Traditional Acupuncture (N =22) vs Shame Acupuncture (N =28)	4 weeks	Low pain sensitivity (LPS), vs sensitivity (HPS), reduced clinical pain response to SA (change in mean [standard deviation (SD)]: HPS - 8.65 [7.91]; LPS - 2.14 [6.68]; p = 0.03). Not the case for TA (HPS - 6.90 [4.51]; LPS - 6.41 [9.25]; p = 0.88). SA-treated patients who were more sensitive also had greater baseline levels of insular Glx than patients who were less sensitive (Glx mean [SD]: HPS 11.3 [1.18]; LPS 10.2 [0.54]; p = 0.04).	"Pressure-pain testing may identify patients who are less likely to respond to SA. This effect may relate to the levels of brain excitatory neurotransmitters."	Data suggests pressure pain testing "may" identify patients less responsive to shame acupuncture (SA) which may be due to different brain neurotransmitter concentration.
Targino, RA 2008 (Score = 7)	Fibromyalgia	RCT	No sponsorship, no mention of COI	N = 58 With FM	58 females; Mean age 51.7	Acupuncture together with tricyclic antidepressants and exercise; 20 sessions of acupuncture, twice weekly, 20 mins each. .25 X 40 mm needles Ex-HN-3 and bilateral LR3,	2 years	3 months (T1) Acupuncture vs Control VAS 5.0 (0.0–10.0) vs 8.0 (4.0–7.0) (p < 0.00) TePsN 12.5 (3–18) vs 17.0 (7–18) (p < 0.001) PPT18 3.53 (0.69) vs 2.84 (0.53) (p < 0.001)	"Addition of acupuncture to usual treatments for fibromyalgia may be beneficial for pain and quality of life for 3 months after the end of treatment. Future research is needed to evaluate the specific effects of acupuncture for fibromyalgia."	Data suggests acupuncture may benefit FM patients in addition to conventional treatment (TCA, exercise and re therapy

						LI4, PC6, GB34 and SP6 points (30). Needle penetration was 10–30 mm without extra rotational or manual stimulation after needle insertion. 12.5-75 mg of tricyclic antidepressants per day. 30 min of walking 30 mins mental relaxation. Twice weekly stretching exercise. (N =34) Vs tricyclic antidepressants and exercise (N =24)		6 months (T2) Acupuncture vs Control VAS 7.0 (2.0–10.0) vs 7.5 (3.0–10.0) (p = 0.18) TePsN 14.0 (3–18) vs 16.0 (10–18) (p = 0.016) PPT 18 3.47 (0.70) vs 2.90 (0.55) (p = 0.002) 12 months (T3) Acupuncture vs Control VAS 7.0 (0.0–10.0) vs 7.0 (3.0–10.0) (p = 0.65) TePsN 15.0 (5–18) vs 15.0 (12–18) (p = 0.47) PPT18 3.19 (0.86) vs 3.05 (0.47) (p = 0.46) 24 months (T4) Acupuncture vs Control VAS 7.0 (0.0–10.0) vs 8.0 (2.0–10.0) (p = 0.58) TePsN 15.0 (6–18) vs 16.0 (7–18) (p = 0.16) PPT18 3.18 (0.80) vs 3.05 (0.88) (p = 0.60)		
Deluze, C 1992 (Score = 6.5)	Fibromyalgia	RCT	No mention of sponsorship or COI.	N= 70 with FM	54 Females 16 males; Mean age 47.5	Electro acupuncture; 6 sessions over 3 weeks. Current of 10 volts at 1000 ohm	3 weeks	P value for intergroup difference after treatment. Pain threshold (p = 0.0303) Regional pain score (p =	"Electroacupuncture is effective in relieving symptoms of fibromyalgia. Its potential in long term management should now be studied."	Data suggest acupuncture significant improve almost all outcome measures in FM patients (pain sleep quality

						frequency 1-99 Hz intensity of current 10 mA. (N = 36) vs Sham procedure (N = 34)		0.05700) sleep quality (p = 0.0782) # Of analgesic tables during last week. (p = 0.945)		number of analgesics morning stiffness not improved.
Harris, R 2005 (Score = 6)	Fibromyalgia	RCT	Sponsorship from the National Institutes of Health, the Department of Defense, Grant from Georgetown University GCRC. No mention of COI.	N = 114 with FM	106 females, 8 males; Mean age 47	Traditional site with manual stimulation (T/S) (N =29) vs Traditional site without stimulation (T/O) (N =30) vs Nontraditional site with stimulation (N/S) (N =28) vs Nontraditional site with no stimulation (N/O) (N =27)	15 weeks	Mean pain, fatigue, and function. Week 3, 8, 13: t= 1.03 (p = 0.307) Location (weeks 3, 8, 13t 1.03; (p =0.307) or location (weeks 3, 8, 13: t = 0.76; (p = 0.450). Model 2 binary response pain variable for either needle stimulation(weeks 3, 8, 13:2 3.60; (p = 0.058) or location (Weeks 3, 8, 13: 2 0.20; (p = 0.657).	"Although needle insertion led to analgesia and improvement in other somatic symptoms, correct needle location and stimulation were not crucial."	Data suggests that all groups experienced improved pain but that the precise location of the needle placement was not critical.
Assefi 2005 (6.0)	Fibromyalgia	RCT	Sponsored by grant from the National Center for Complementary and Alternative Medicine. Authors Assefi, Goldberg,	N = 96 who met the 1990 American College of Rheumatology fibromyalgia criteria	94 female, 2 male. Mean age overall 47 years	Directed acupuncture (n = 25) vs Sham unrelated condition (n = 24) vs sham needling (n = 24) vs simulated acupuncture (n = 23). All	12 weeks	Mean pain rating in those who received acupuncture not statistically different from mean in pooled sham acupuncture group (mean between-group difference 0.5 cm, 95% CI (0.3 cm, 1.2 cm))	"Acupuncture was no better than sham acupuncture at relieving pain in fibromyalgia."	Data suggest similar in efficacy.

			Smith, and Buchwald all received grants.			participants received treatment sessions twice a week 12 weeks				
Hadianfard, 2012 (Score = 4.5)	Fibromyalgia	RCT	Sponsored by grants from the national center for complementary and alternative medicine. COI grants. Potential Financial Conflicts of Interest: Grants received: N.P. Assefi, J. Goldberg, W.R. Smith, D. Buchwald (National Center for Complementary and Alternative Medicine).	N=99 Patients with fibromyalgia.	94 females, 6 males; Mean age 47.	Directed Acupuncture for Fibromyalgia (n = 25). vs Sham acupunctures (n total = 74); Needling for an Unrelated Condition (n = 25), Sham Needling (n = 24), Simulated Acupuncture (n = 25)	12 weeks	Adverse effects; 37% experienced discomfort at needle site, 30% had bruising, 3% reported nausea, .3% felt faint. Patients in simulated acupuncture; 29% had less discomfort then those assigned to directed acupuncture 61%, or acupuncture for unrelated condition 70%, or sham 64% (p = 0.02) Less bruising as reported in simulated acupuncture 10%, direct acupuncture 52%, acupuncture for unrelated condition 74%, sham needling 68% (p = 0.001). directed acupuncture group with the pooled sham-intervention group were 0.5 cm (95% CI, -0.3 to 1.2 cm) for pain (P = 0.2), 0.5 cm (CI, -0.2 to 1.2 cm) for fatigue (P = 0.19), -0.5 cm (CI, -1.3 to 0.2 cm) for sleep quality (P = 0.18), -0.3 cm (CI, =1.0 to 0.3 cm) for overall well-being (P = 0.2), -0.4 (CI, -2.3 to 1.5) for the Short	"Acupuncture was no better than sham acupuncture at relieving pain in fibromyalgia."	Data suggests acupuncture better then fluoxetine for FM pain at 4 weeks and positive effects diminish at one year post intervention. Inclusion data do not preclude prior SSRI treatment raising concerns of bias.

								Form-36 Physical Component Summary score (P = 0.2), and -1.5 (CI,-4.0 to 1.0) for the Short Form-36 Mental Component Summary score (P = 0.2).		
Harris, R 2009 (Score 4.5)	Fibromyalgia	RCT	Sponsorship by funding from the Department of Army Grands and the National institutes of Health. No mention of COI.	N = 20 with FM	20 females; mean age 44.3	Nine traditional acupuncture (N =10) Vs nine non-skin penetrating sham acupuncture (N = 10)	Change in clinical pain,	mean diff(SD) treatment – baseline; −3.45(7.39), (p<0.05) sensory and pain affect subscales (Sensory Score: −2.65 (5.98), (p=0.06); Affective Score: −0.80 (2.26), (p = 0.13). Both TA and SA resulted in clinically meaningful reductions in pain (SF MPQ Total Score mean diff(SD); TA: −4.00 (6.72); SA: −2.90 (8.33)), differences in pain reduction between TA and SA (p>0.50)	"Overall we find that traditional acupuncture therapy evokes an increase in MOR availability over both short and long periods."	Data suggest acupuncture involved both long and short term increase in 140R procedure not found in sham group and long term increase were associated with great pain reduction.

Evidence for Manipulation and Mobilization

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Castro-Sanchez 2014 (5.0)	Manipulation and mobilization	RCT	No mention of sponsorship. No COI.	N = 89	48 females, 41 males. Mean age is	Experimental Group: received manual therapy (N = 45) vs. Control Group: no intervention (N = 44)	5-weeks	ANCOVA showed significant group and time interactions for pain (F = 7.63, P = 0.003). Tender point count: (F = 12.69, P = 0.001). McGill PRI (F = 9.35, P = 0.003). McGill PPI (F = 7.63, P = 0.003). FIQ (F = 19.57, P < 0.001).	"Manual therapy protocol was effective for improving pain intensity, widespread pressure pain sensitivity, impact of FMS symptoms, sleep quality, and	Usual care bias. Data suggest improvement in pain intensity pressure, pain sensitivity quality of sleep and depression.

									depressive symptoms."	
Moustafa IM, 2015 (4.5)	Manipulation and mobilization	RCT	No sponsorship or COI.	N = 120 patients with fibromyalgia.	The mean age of the experimental group is 53.5 years. 35 males, 25 females. The mean age of the control group is 51.4 years. 33 males, 27 females.	Experimental Group (n=60) Vs Control Group (n=60)	Baseline, 12 weeks, and 1 year after the 12 week treatment period.	The FIQ score pretreatment for the experimental and control groups was 70.9 ± 4.4 and 71.3 ± 5.8, respectively. The FIQ score posttreatment for the experimental and control groups was 44.1 ± 7.2 and 43.6 ± 7.4, respectively. P=.4. the FIQ score at one-year follow up for the experimental and control group was 9.3 ± 3.4 and 47.9 ± 7.7, respectively, p<0.0005.	"The addition of the upper cervical manipulative therapy to a multimodal program is beneficial in treating patients with FMS."	CBT + CMT vs. edn. Unclear If CMT or CBT was responsible for improved symptoms in patients.

Evidence for Massage

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ekici, G 2009 (Score = 4.5)	Fibromyalgia	RCT	No mention of sponsorship or COI.	N = 50 with primary fibromyalgia (PFM)	50 females; mean age 37.905	Manual lymph drainage therapy (MLDT) (N = 25) vs Connective tissue massage (CTM) (N = 25)	3 weeks	VAS score MLDT vs CTM. 1.49 ± 1.19, 2.59 ± 2.05 (p = .071). Energy MLDT vs CTM. 18.72 ± 19.73, 27.26 ± 33.63 (p = .531) Pain MLDT vs CTM. 9.66 ± 9.52, 17.10 ± 13.84 (p = .057). FIQ-Total MLDT vs CTM. 18.88 ± 8.30, 28.55 ± 13.46 (p = .010)	"For this particular group of patients, both MLDT and CTM appear to yield improvements in terms of Pain, health status, and HRQoL. The results indicate that these manual therapy techniques might be used in the treatment Of PFM. However, MLDT was found to be more effective than CTM according to some sub items of FIQ (morning Tiredness and anxiety) and FIQ total score. Manual lymph drainage therapy might be preferred; however, further long-term Follow-up studies are needed."	Data suggest comparable efficacy for pain health status and QoL.

Evidence for Myofascial Release

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Castro-Sánchez 2011 (Score = 5)	Fibromyalgia	RCT	No sponsorship. No mention of COI.	86 patients with FM	No mention of sex; Mean age 54.4	10 myofascial release modalities (N = 45) vs placebo group received sham short-wave and ultrasound electrotherapy. (N = 41)	20 weeks	(P < 0.05) in painful tender points, McGill Pain Score (20.66.3, P<0.032), physical function (56.1017.3, P<0.029), and clinical severity (5.081.03, P<0.039). At six months post intervention, the experimental group had a significantly lower mean number of painful points, pain score (8.251.13, P<0.048), physical function (58.6016.30, P<0.049) and clinical severity (5.280.97, P<0.043).	"The results suggest that myofascial release techniques can be a complementary therapy for pain symptoms, physical function and clinical severity but do not improve postural stability in patients with fibromyalgia syndrome."	Patients unblended. Data suggest short term benefit but at 1 year these benefits were significantly reduced.

Evidence for Hot and Cold Therapies

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Clarke-Jenseen, A 2014 (6.0)	Fibromyalgia	RCT	Sponsorship by the Section for Climate Therapy, Oslo University Hospital, Rikshospitalet. No mention of COI.	N = 132 with FM	119 females, 10 males; mean age 45.	Warm climate N = 43 vs Cold climate N = 42 vs Control N = 44	12 months.	TPC between the warm and cold climate groups 1 year 1.7 (–2.9 to –0.5) (*p* = 0.002) TPC between the warm and cold climate groups 1 year after the intervention was –1.7 (–2.9 to –0.5) (p = 0.002). Between the warm climate and the control	"A rehabilitation programme for fibromyalgia may have a long-term effect on pain, as measured by TPC and pain distribution, when applied in a warm climatic setting, and may improve physical function regardless of the	Data suggest a rehabilitation program for fibromyalgia as measured by TPC and pain distribution but physical function improvements occur regardless of climate (warm or

								groups was –2.2 (–3.3 to –1.0) (p < 0.001) Three months mean difference warm vs cold climate groups in pain distribution was –12 (–20 to –5) (p < 0.001) warm climate vs control group –11 (–18 to –3) (p < 0.002). VAS pain measures the intensity of pain, and this was reduced by 1.2 (2.2–0.1) (p = 0.023)	climatic setting."	cold) 1 year post intervention.
Thomas-Carus, P 2008 (Score = 4.5)	fibromyalgia	RCT	Sponsorship by co-financing by the Regional Government of Extremadura. No mention of COI.	N = 30 with FM	30 females; Mean age 50.8	Exercise training in a waist-high pool of warm water (33ºC) 3 times per week during the 8-month period. Each session lasted for 1 h and included 10 min of warming up with slow walks and easy movements of progressive intensity, 10 min of aerobic exercises at 60–65% of maximal heart rate (Hrmax), 20	8 months	Total FIQ Exercise vs Control 5.2 vs 6.5 (p = 0.017) Hand grip strength 39.1 vs 34.2 (p = 0.249 10-step stair-climbing weightless 4.1 vs 5.1 (p = 0.003) 10-step stair-climbing with 10kg weight 4.5 vs 6.5 (p = 0.002) 10-m maximal walking speed 1.9 vs 1.9 (p = 0.0060	"Eight months of supervised exercise in warm water was feasible and led to long-term improvements in physical and mental health in patients with fibromyalgia at a similar magnitude to those of shorter therapy programmes."	Data suggest at 8 months' implementation of regular and moderate intensity exercise. In warm water had a posture impact on both mental and physical functioning in MF patients.

						min of overall mobility and lower limb strength exercises using water resistance (4 sets of 10 repetitions of unilateral flexion and extension of the knee at a slow pace with the body in a vertical position) N = 15 vs control N = 15				
Brockow, T 2007 (Score = 4.5)	Fibromyalgia	RCT	No mention of Sponsorship or COI.	N = 139 with FM	135 females, 4 males; mean age 49	Mild water-filtered near infrared whole-body hyperthermia (N1-WBH) +Multimodal Rehabilitation (MR) heating-up to 38.1 degrees C body core temperature followed by a 15 min heat retention period twice weekly for 3 weeks. vs MR	6 months	Effective pain (N1-WBH) + MR vs MR End of intervention -11.4 vs -6.2 3 mo. -8.2 vs -3.1 6 mo. -6.2 vs -2.1 (p = 0.001) Sensory pain End of Intervention -3.9 vs -1.4 3 mo. -3.7 vs +0.4 6 mo. -2.5 vs +0.9 (p < 0.0005).	"Our study showed that NI-WBH and MR is superior to MR only in relation to pain control and amelioration of FM-specific quality of life."	Data suggest N1-WBH plus MR is better than MR alone for affective and sensory pain in fibromyalgia.

Evidence for Interferential current and Ultrasound

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Moretti F 2012 (5.0)	Fibromyalgia	RCT	Supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) - Process 05/56816-2. No COI.	N= 50 patients with fibromyalgia	Mean age: 52.9 years	G1 = once a week treatment (n=25) Vs. G2 = twice a week treatment (n=25)	Once a week or twice a week in Twelve week period	G1 and G2 showed a significant improvement in Visual Analogue Scale ($p<0.0001$ and $p<0.0005$, respectively), Tender Points ($p<0.005$ and $p<0.001$, respectively), Fibromyalgia Impact Questionnaire and Post Sleep Inventory ($p<0.005$ and $p<0.05$, respectively). However, there was no significant difference between the two groups in all performed analyses.	"Although CT can be an important tool in the treatment of woman with FM, there is no significant difference between one or two applications per week. Because one application is as effective as two applications per week, the treatment can be cheaper and more affordable"	Data suggest combination therapy provided benefit for FM patients in terms of pains, sleep quality and overall Q.L but there was no advantage to increasing the frequency of session raising question of efficacy.

Evidence for Pulsed Electromagnetic Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Sutbeyaz S (7.0)	Fibromyalgia	RCT	No mention of sponsorship or COI.	N= 46 women with Fibromyalgia	Mean age: 41.9 years ; 46 females	low-frequency pulsed electromagnetic field (PEMF) therapy group (n=28) Vs.	follow-up at 12 wk	The PEMF group showed significant improvements in FIQ, VAS pain, BDI score, and SF-36 scale in all domains at the end of therapy. These improvements in FIQ, VAS pain, and	"The findings of this study support the need for future investigations of PEMF therapy for the treatment of FM. Such studies should explore the duration of the effects of	Data suggest low frequency PEMF therapy may benefit FM patients by decreasing pain, fatigue and improving overall well-being.

						the sham group (n=28) participated in therapy, 30 minutes per session, twice a day for 3 weeks		SF-36 pain score during follow-up. The sham group also showed improvement were maintained on all outcome measures except total FIQ scores after treatment. At 12 weeks follow-up, only improvements in the BDI and SF-36 scores were present in the sham group.	PEMF by performing longer-term follow-up evaluations, and also by using different parameters of stimulation. In conclusion, PEMF therapy may improve function, pain, fatigue, and global status in FM patients and may offer a potential therapeutic adjunct to current FM therapies in the future."	

Evidence for Microcurrent Cranial Electrical Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Taylor A 2011 (6.0)	Fibromyalgia	RCT	Supported by an intramural award from the University of Virginia School of Nursing and by the Center for the Study of Complementary and Alternative Therapies	N= 46	Mean age: 50.8 years; (3 males, 43 females)	Group A with Active cranial Electrical stimulation (CES) device. (N = 17) vs Group B with sham CEA device (N = 14) vs. Group C Usual care alone (N=15)	At 6 month	Those individuals using the active CES device had a greater decrease in average pain (p = .023), fatigue (p = .071), and sleep disturbance (p = .001) than individuals using the sham device or those receiving usual care alone over time. Additionally, individuals using the active CES device had improved functional status versus the sham device and UC groups over time (p = .028).	"Based on the findings of this study, the use of CES shows promise in the management of FM symptoms, given the decreased pain and significant improvements in other symptoms and functional status. Ideally, patients with FM would be able to obtain a prescription for the device from their health care provider, potentially allowing for coverage of the cost of the	No table of results. Graphs appear to suggest improved pain in CES- devise group and improved sleep, fatigue, reduction and overall functional status improvement.

									device by health insurance. CES devices could be obtained from the company, pharmacy, or the health care provider, as with other medical devices. It is envisioned that the device would be used for symptom management in the home setting by patients with FM based on evidence-based recommendations from their health care providers. Additional analyses of the data from the current study will be conducted to correlate symptom assessments with psychological factors. Sleep actigraphy data also will be analyzed for effects on objective measures of sleep."	

Evidence for Transcranial Direct Current Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Villamar M 2013 (6.5)	Fibromyalgia	patient- and assessor-blind, sham-controlled, crossover trial	Funded by a Translational Research Award from the Wallace H. Coulter Foundation. No mention of COI	N = 18	Mean age: 50.3 years; 15 females, 3 males	18 patients were randomized to undergo single 20-minute sessions of anodal, cathodal, and sham HD-tDCS at 2.0 mA in a counterbalanced fashion	Assessments were done during 5 visits. Pain levels were checked at baseline, immediately after stimulation and thirty minutes after stimulation.	A decrease in mean overall pain scores assessed before, immediately after, and 30 minutes after each stimulation was observed over time. significant pain improvement across interventions was detected (P for global test = .004). When evaluating changes in perceived pain immediately after stimulation, only cathodal HD-tDCS led to significant improvement as compared to sham (P = .012). However, both active conditions induced significant mean pain reduction 30 minutes after the end of the stimulation (anodal versus sham, P = .031; cathodal versus sham, P = .001)	"A single 20-minute session of active 4_1-ring HD-tDCS, with a radius of approximately 7.5 cm between electrodes and delivering 2.0mAto the left M1, provided significant overall pain relief in FM patients as compared to sham stimulation, regardless of current polarity. This protocol was well tolerated in this patient population, in whom it induced no moderate or serious adverse effects. Although these findings are not sufficient to definitely establish 4_1-ring HD-tDCS as a therapy for FM, this trial represents an initial step toward the study of a potentially effective intervention."	Data suggest a 20 minute session of HD+DCS (regardless of polarity, decreased pain in FM patients.

Mendonca M 2011 (6.5)	Fibromyalgia	RCT	F.F. is supported by grant from NIH R21DK081773. The authors have no conflicts of interest	N=30 patients with fibromyalgia	mean age of 43.2 years; (28 females, 2 males)	Group cat-M1–cathodal stimulation of the left M1 region Vs 2) Group cat-SO–cathodal of the right supra-orbital region vs. 3) Group ano-M1–anodal stimulation of the left M1 vs 4) Group ano-SO–anodal stimulation of the right supraorbital Region Vs 5) Sham stimulation group. (Each group n=6)	Not mentioned	There was significant pain reduction in cathodal-SO and anodal-SO groups indexed by VNS. For PPT there was a trend for a similar effect in anodal-SO group. Computer simulation indicated that the M1-extracephalic montage produced dominantly temporo-parietal current flow, consistent with lack of clinical effects with this montage. Conversely, the SO-extracephalic montage produced current flow across anterior prefrontal structures, thus supporting the observed analgesic effects.	"In conclusion, it was observed that the stimulation of the prefrontal cortex with tDCS, irrespective of the polarity of the electrode, resulted in short-term pain decrease in patients with fibromyalgia, and that the stimulation of the M1 area using the extracephalic electrode had no immediate analgesic effect. The usage of extracephalic electrodes with motor cortex or prefrontal cortex electrodes activates different cortical areas compared with the use of 2 electrodes over the scalp; therefore, we showed a match between currents induced in areas associated with pain matrix and pain reduction. These findings should be taken into consideration in future tDCS studies."	Data suggest decreased pain in tDCS group, but no pain longer term follow up

Fregni F 2006 (6.5)	Fibromyalgia	RCT	Dr. Fregni's work was supported by the NIH (grant K30-HL-04095 from the Harvard Medical School Scholars in Clinical Science Program). Dr. Pascual-Leone's work was supported by the NIH (grant K24-RR018875)	N=32 patients with fibromyalgia	Mean age: 52 years; all females	Sham stimulation (n=10) Vs. Real tDCS with the anode centered over the primary motor cortex M1) or the dorsolateral prefrontal cortex (DLPFC) (2 mA for 20 minutes on 5 consecutive days) (both groups, n=11)	After 3 weeks of treatment	Anodal tDCS of the primary motor cortex induced significantly greater pain improvement compared with sham stimulation and stimulation of the DLPFC ($P < 0.0001$). Although this effect decreased after treatment ended, it was still significant after 3 weeks of follow up ($P =0.004$). A small positive impact on quality of life was observed among patients who received anodal M1 stimulation. This treatment was associated with a few mild adverse events, but the frequency of these events in the active-treatment groups was similar to that in the sham group. Cognitive changes were similar in all 3 treatment groups.	"Our findings provide initial evidence of a beneficial effect of tDCS in fibromyalgia, thus encouraging further trials."	Only 5 day study. Some outcomes data concerning for possible randomization failure.
Fagerlund A 2015 (5.5)	Fibromyalgia	RCT	This study was funded by a grant from the Norwegian Extra Foundation for Health and Rehabilitation through the Norwegian	N= 48 patients with fibromyalgia	Mean age:48.5 years; (24 females, 3 males)	Received active tDCS (n=24) Vs. Sham tDCS (n=24)	pretreatment period of 30 days, 5 days of tDCS stimulation, and posttreatment period of 30 days.	Adverse effects were registered using a standardized form. A small but significant improvement in pain was observed under the active tDCS condition but not under the sham condition. Fibromyalgia-related daily functioning improved in the active tDCS group compared with the sham	In conclusion, the results of this study suggest that tDCS reduces the pain levels in patients with FIM, but the effect sizes are small and unlikely to reflect clinically important change. The patients experienced no serious adverse	Data suggest tDCS may reduce pain associated with FM, only 5 day study.

			Fibromyalgia Association to Dr Per M. Aslaksen. The authors declare no conflicts of interest.					group. The stimulation was well tolerated by the patients, and no significant difference in the adverse effects between the groups was observed.	effects, indicating that tDCS with an intensity of 2 mA over 5 consecutive days was well tolerated.	
Roizenblatt S 2007 (5.5)	Fibromyalgia	RCT	Suely Roizenblatt is supported by FAPESP—CEPID 98/14303–3 and AFIP. Felipe Fregni is supported by grants from NIH (DK071851-01) and the Harvard University David Rockefeller Center—Jorge Paulo Lemann Fellowship.	N= 32 patients with fibromyalgia	Mean age: 54.2 years. (females only)	sham stimulation (n=10) vs. active tDCS with the anode centered over M1 or DLPFC (2 mA, 20 minutes for five consecutive days). (for both, n=11)	For 21 days	Anodal tDCS had an effect on sleep and pain that was specific to the site of stimulation: such as that M1 and DLPFC treatments induced opposite effects on sleep and pain, whereas sham stimulation induced no significant sleep or pain changes. Specifically, whereas M1 treatment increased sleep efficiency (by 11.8%, *P* = 0.004) and decreased arousals (by 35.0%, *P* = 0.001), DLPFC stimulation was associated with a decrease in sleep efficiency (by 7.5%, *P* = 0.02), an increase in rapid eye movement (REM) and sleep latency (by 47.7%, *P* = 0.0002, and 133.4%, *P* = 0.02, respectively). In addition, a decrease in REM latency and increase in	"We show for the first time that a novel treatment with noninvasive brain stimulation improves sleep architecture in patients with fibromyalgia and this improvement is correlated with pain reduction. These findings support the notion that fibromyalgia is associated with focal changes in brain activity that are responsible for sleep disturbances and pain."	Data suggest tDCS has positive benefit on the sleep and pain of FM patients

								sleep efficiency were associated with an improvement in fibromyalgia symptoms (as indexed by the Fibromyalgia Impact Questionnaire). Finally, patients with higher body mass index had the worse sleep outcome as indexed by sleep efficiency changes after M1 stimulation.		
Mendonca M 2016 (4.5)	Fibromyalgia	RCT	This study was supported by the Brazilian funding agencies Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP 2012/06519-5).	N= 45 patients with fibromyalgia	Mean age:47.4 years, 44 females, 1 male	**tDCS/AE**, which received active intervention of aerobic exercise training and active tDCS intervention (n=15) vs. **AE**, which received active intervention of aerobic exercise and placebo tDCS (n=15) Vs. **tDCS**, which received placebo AE and active intervention for tDCS.(n=15)	All variables were measured 1 week before the beginning of the intervention (baseline), after intervention period (T2) and during the periods of follow-up conducted 1 month (T3) and 2 months (T4) after the end of the intervention period	There was a significant effect for the group-time interaction for intensity of pain, demonstrating that tDCS/AE was superior to AE [*F*= (13,364) =2.25, *p*=0.007] and tDCS [*F*= (13,364) =2.33, *p*=0.0056] alone. *Post-hoc* adjusted analysis showed a difference between t DCS/AE and tDCS group after the first week of stimulation and after 1 month intervention period (*p*=0.02 and *p*=0.03,respectively). Further, after treatment there was a significant difference between groups in anxiety and mood levels. The combination treatment effected the greatest response. The three groups had no differences regarding responses in motor cortex plasticity, as	Based on these findings, the three groups showed positive effects in many variables, such as pain relief, quality of life, depression, and anxiety, but there was a larger effect that was associated with the combination treatment. The simultaneous effect of the combination treatment on pain and depression levels in fibromyalgia should prompt larger trials on the effects of this modality with longer follow-up periods.	Data represents subjects were blinded but study design makes it impossible to blind participants. Data suggest combination of aerobic exercise in combination with tDCS may improve pain, anxiety, and mood in FM patients.

								assessed by TMS. The combination of tDCS with aerobic exercise is superior compared with each individual intervention (Cohen's effect sizes>0.55).		

Evidence for Transcranial Magnetic Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Baudic S 2013 (7.0)	Fibromyalgia	RCT	No sponsorship. No COI.	N = 38 non depressed fibromyalgia patients	Mean age: 50.5 years	Active rTMS (repetitive transcranial magnetic stimulation) (N = 20) vs sham stimulation (N =18)	Follow up visit at week 25	Neuropsychological tests were performed immediately before stimulation, to evaluate episodic memory, selective and divided attention and executive functions at baseline, week 3 (after 7 rTMS sessions) and week 11 (after 11 rTMS sessions). The actively treated and sham-treated groups were similar in terms of clinical and neuropsychological variables at baseline. No difference in overall neuropsychological performance with respect to baseline was found between these two groups, but a significant improvement over time was observed in the rTMS group, for several	"In conclusion, we found that 11 sessions of high-frequency rTMS (10 Hz) at 80% of the RMT applied to the left primary cortex resulted in no significant cognitive deterioration in patients with chronic pain. Instead, there was a tendency toward an improvement of performance in several tests for the active treatment group. This study confirms that chronic rTMS stimulation is a safe treatment option for patients with fibromyalgia, including those with cognitive	Data suggest at 3 months rTMS results comparable to sham (lack of efficiency) for improving cognitive function in chronic pain patients.

								measurements of attention/executive function	impairment at baseline."	
Passard A 2007 (6.5)	Fibromyalgia	RCT	No mention of COI or sponsorship.	N=30 patients with fibromyalgia	Mean age: 53.9 years, 29 females, 1 male	Active rTMS group (n=15) vs. Sham-stimulation group (n=15) applied to the left primary motor cortex in 10 daily sessions	Follow up was up to 2 weeks after treatment ended.	Pain intensity was similar in the two groups at baseline and rTMS had a significant effect on average pain intensity score between baseline and day 15 (P<0.05) The increase in pain thresholds at these two tender points was correlated with the decrease in average pain intensity on D15 (r = 0.49, P<0.05). Active rTMS induced a significant decrease in pain interference with general activity, sleep and walking until D30. Mean depression and anxiety scores (as measured on the HADRS, BDI and HAD scales) were similar in the two treatment groups at baseline and were not significantly affected by active or sham stimulation.	"Our data indicate that unilateral rTMS of the motor cortex induces a long-lasting decrease in chronic widespread pain and may therefore constitute an effective alternative analgesic treatment for Fibromyalgia."	Data suggest unilateral rTMS of the motor cortex of FM patients decreases chronic pain

Boyer L 2014 (6.5)	Fibromyalgia	RCT	Supported by Inserm (Centre d'Investigation Clinique, CIC, Hôpital de la Conception, Marseille) and AP-HM (AORC 2008/01). International Standard Randomized Controlled Trial Number: NCT00697398. No COI	N= 38 patients with fibromyalgia	Mean age: 48.2 years; 37 females, 1 male	High-frequency repetitive transcranial magnetic stimulation rTMS (n= 19) Vs. sham stimulation (n= 19), applied to left primary motor cortex in 14 sessions over 10 weeks. Primary	at baseline, week 2, and week 11	At week 11, patients of the active rTMS group had greater QoL improvement in the FIQ (p 5 0.032) and in the mental component of the SF-36 (p 5 0.019) than the sham stimulation group. No significant impact was found for other clinical outcomes. Compared with the sham stimulation group, patients of the active rTMS group presented an increase in right medial temporal metabolism between baseline and week 11 ($p < 0.001$), which was correlated with FIQ and mental component SF-36 concomitant changes ($r= -0.38$, $p = 0.043$; $r = 0.51$, $p = 0.009$, respectively)	"Our study shows that rTMS improves QoL of patients with fibromyalgia. This improvement is associated with a concomitant increase in right limbic metabolism, arguing for a neural substrate to the impact of rTMS on emotional dimensions involved in QoL."	Data suggest at 3 months rTMS may improve QoL in fibromyalgia patients
Mhalla A 2011 (6.0)	Fibromyalgia	RCT	This study was supported by grants from the ''Fondation APICIL'' and the ''Fondation de France. No COI.	N= 40 patients with fibromyalgia	Mean age: 50.5 years; 40 females, zero males.	one receiving active repetitive transcranial magnetic stimulation (rTMS) (n = 20) Vs. the other, sham stimulation (n = 20), applied to the left primary motor cortex	the follow-up visit in week 25 (1 month after the last stimulation).	Active rTMS significantly reduced pain intensity from day 5 to week 25. These analgesic effects were associated with a long-term improvement in items related to quality of life (including fatigue, morning tiredness, general activity, walking, and sleep) and were directly correlated with changes in intracortical inhibition.	In conclusion, the data presented here indicate that rTMS may be a valuable new therapeutic option in patients with fibromyalgia. Future studies should investigate whether long-lasting analgesic effects can also be obtained in other chronic pain syndromes	Data suggest the analgesic effects of rTMS were sustained at 25 weeks.

Short E 2011 (5.0)	Fibromyalgia	RCT	Funding for this pilot project, under Multidisciplinary Clinical Research Center grant P60 AR049459, was generously provided by the Office of the Provost and Vice-President for Research	N= 20 patients with fibromyalgia	Mean age: 53.0 years; 17 females,3 males	Active treatment of Transcranial magnetic stimulation (TMS): 4000 pulses at 10Hz TMS (n= 10) Vs. Sham arm (n=10)	At week 1,2, 3 and 4	No statistically significant differences between groups were observed. Patients who received active TMS had a mean 29% (statistically significant) reduction in pain symptoms in comparison to their baseline pain. Sham TMS participants had a 4% nonsignificant change in daily pain from their baseline pain. At 2 weeks after treatment, there was a significant improvement in depression symptoms in the active group compared to baseline. Pain reduction preceded antidepressant effects. TMS was well tolerated, with few side effects.	"This is the first published rTMS trial stimulating LDLPFC to assess for reductions in fibromyalgia pain. In total, the data lends inconclusive, but suggestive support to the hypothesis that high frequency rTMS at the LDLPFC, as an adjunct to pharmacotherapy, may reduce fibromyalgia pain. Further work is needed to determine if rTMS may have pain modulation effects for fibromyalgia in a larger clinical trial"	Pilot study data suggests a trend towards reduction of pain symptoms and depression but this was not significant.
Lee S 2012 (4.5)	Fibromyalgia	RCT	No COI. No mention of sponsorship	N=15 women with fibromyalgia	Mean age: 49.9 years; all females.	Low frequency (1Hz) stimulation (LF) vs. High frequency (10Hz) stimulation (HF) Vs. Sham stimulation	At baseline, after rTMS and 1 month after treatment.	In LF group, the back depression inventory scores significantly decreased from baseline to 1 month after rTMS. The visual analog scale and Korean version of the fibromyalgia impact questionnaires scores significantly decreased immediately after rTMS. In the HF group the visual analog scale and back depression inventory scores were significantly	"Low frequency rTMS may play a role in the long term treatment of fibromyalgia. Notably, the findings of this study are the first to show that the right dorsolateral prefrontal cortex or the left motor cortex rTMS could have an anti-depressive and pain modulating effect in patients with fibromyalgia."	Small sample. Data suggest no efficacy c/w sham

						(Each group, n=5) Each patient was treated with 10 sessions (5 times per week for 2 wks)		decreased immediately after rTMS		
Carretero B 2009 (4.0)	Fibromyalgia	RCT	This study was supported by grant SEJ2007-62312 (MICINN-FEDER Funds). No mention of COI.	N= 26 patients with fibromyalgia	Mean age: 51.2 years, 24 females, 2 males.	Real TMS (n=14) Vs. Sham TMS (n=12) Patients received 20 sessions of real or sham transcranial magnetic stimulation of the right dorsolateral prefrontal cortex.	Follow up for 6 weeks	Both treatment groups (real and sham) improved their scores in some of the scales (Fibro-Fatigue and Clinical Global Impression), although there were no differences between them. No improvements were observed in the Likert Pain Scale in either of the groups.	"With the methodology used in this study, patients with fibromyalgia and major depression who received real magnetic stimulation did not present significant differences in symptoms with respect to those who received sham magnetic stimulation"	Data suggest a lack of efficacy.

Evidence for Low-Level Laser Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Panton 2013 Score: 5.5	Chronic, Fibromyalgia	RCT	Sponsorship by Litecure. No COI.	N = 20 participants with fibromyalgia	Mean age 53. 0 males, 38 females.	Laser (20% 810nm, 80% 980 nm at 10 W, 10.63J/cm^2) heat therapy (LHT, N = 20), vs sham heat therapy (SHT, N = 18). Both therapies were 15 min/session, 2 session/w for 4 weeks.	Follow-up at 2 weeks.	Significant results seen for LHT group in the FIQ pain subscale ($p \leq 0.05$), upper body flexibility ($p \leq 0.05$), and time effects for functionality measured by the FIQ (63 ± 20 to 57 ± 18 units) after treatment, with no change in SHT group.	"The use of a Class IV laser and/or heat therapy reduces pain and improves functionality in women with FM. In addition, Class IV laser therapy significantly reduced FM impact by decreasing pain measured by the subscale of the FIQ and increased the upper body flexibility domain of functionality compared to the sham and heat group."	Data suggest lack of efficacy c/w sham.
Ruaro 2014 Score: 5	Chronic, Fibromyalgia	RCT	No mention of sponsorship or COI.	N = 20 participants clinically diagnosed with fibromyalgia	Mean age 41.4. 1 male, 19 females.	Low-level laser therapy (LLLT) 3X/w for 4 weeks (N = 10), vs sham treatment 3X/w for 4 weeks (N = 10)	Follow-up at 4 weeks.	Significant results in both LLLT group (aluminum/gallium/arsenide diode laser, 20 nW, 670 nm wavelength) and sham group (zero watts of laser), for number of reduced 18 tender points ($p=0.0001$, $p<0.0001$, respectively) compared to baseline. Significant improvement in all areas of the Fibromyalgia Impact Questionnaire (FIQ) for LLLT ($p=0.0086$ to $p<0.0001$), and significance in physical impairment and pain of	"This study suggests that LLLT provides relief from the symptoms of fibromyalgia and could be an important therapeutic tool to lessen the impact of the disease, decrease pain, and improve quality of life for patients."	Small sample, baseline date suggest randomization failure.

								the FIQ for sham group (p=0.032 for both). Significant improvement in LLLT compared to sham group in McGill Pain Questionnaire (p=0.0078), and visual analog scale (p=0.002)		
Matsutani 2007 Score: 4.5	Chronic, Fibromyalgia	RCT	No mention of sponsorship, no COI.	N = 20 participants diagnosed with fibromyalgia	Mean age 45.5. 0 males, 20 females	Laser therapy and stretching (LSG, N = 10) group (1h, 2x/w, for 5 weeks of laser, 3J/cm^2, and stretching exercises), vs stretching group (SG, N = 10) only (1h, 2x/w, for 5 weeks of stretching exercises).	Follow-up at 5 weeks.	Statistically significant results compared to baseline were seen in both LSG and SG groups for visual analogue scale (p=0.006, p=0.002), pain threshold increase for tender points (p=0.001, p=0.007), higher Short-Form Health Survey (p=0.001, p=0.000), and lower Fibromyalgia Impact Questionnaire (p=0.039, p=0.006). There were no statistically significant differences between groups.	"The stretching exercises program proposed is efficient to reduce pain and painful sensibility at tender points, thus enhancing patients quality of life. Laser therapy has not shown advantages when added to muscle stretching exercises."	Data suggest stretching is effective in reducing tender point pain and laser therapy has no advantage over stretching exercises.
Vayay 2016 Score: 4.5	Chronic, Fibromyalgia	RCT	No mention of COI or sponsorship.	N = 38 participants diagnosed with fibromyalgia	Mean age 37.47. 0 male, 45 females.	Laser (3 min per 17 painful points, 2J/cm^2 40mw, 850 nm wavelength) group, received laser and exercise program (N = 15), vs placebo laser group, received sham laser and exercise	Follow-up at 15 days and 3 weeks.	Significant results seen in decrease of pain at night for laser, placebo laser, and taping groups (p=0.04, p=0.001, p=0.001 respectively). Significant pain reduction during exercise was found in laser group only (p=0.02). Significant improvement in FIQ for laser, placebo laser, and taping groups (p<0.001, p<0.001, p=0.01 respectively). Significant body flexion flexibility increase in placebo laser	In this study where the impact of the Laser application and taping on pain, function and quality of life of the cases diagnosed with fibromyalgia all treatment groups were found to be effective on different parameters. While it is observed that the three-week Laser and taping in FMS improved the	Data suggest comparable benefits for FM between kinesiotaping and laser but the laser groups reported less pain.

						program (N = 15), vs taping group, received kinesiotaping and exercise program (N = 15). All groups received 5 treatments per week for 3 weeks.		and taping groups (p<0.001, p-0.03), and significant increase in hyperextension flexibility in taping group (p=0.02). Significant improvement in Beck Depression Scale for laser (p=0.01) and taping group (p=0.01).	general health level, depression and anxiety and increase functionality similarly, the Laser application additionally led to decrease in pain level and increase in body flexion flexibility and the taping led to increase in body hyperextension flexibility."	

Evidence for Transcutaneous Electrical Nerve Stimulation (TENS)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Dailey D 2013 (7.0)	Fibromyalgia	RCT (double-blinded randomized, placebo controlled cross-over Design)	Supported by a grant from the Orthopedic Section of the American Physical Therapy Association, the Carver College of Medicine at the University of Iowa, College of Nursing at the University of Iowa,	N = 41 patients with fibromyalgia who have enhanced central excitability and reduced inhibition	Mean age: 49.1 years; females 40, 1 male)	Active TENS application vs. Placebo vs. no TENS Active TENS further divided: Cervical (N =17) vs Lumbar (N = 24)	Not mentioned	The average pain intensity at rest (0–10 scale) before TENS was similar between treatments: active TENS was 5.0 ± 0.5, placebo TENS was 5.0 ±0.4, no TENS was 5.2 ± 0.4. Pain at rest showed no significant difference between treatments: active TENS, placebo TENS or no TENS. Pain with movement (during the 6MWT) was significantly less during active TENS (4.0 ± 0.4) when compared to placebo (4.7 ± 0.4)	"In summary, TENS improved movement pain and fatigue, increased pain thresholds both at and outside of the site of stimulation, and increased conditioned pain modulation. Importantly, the current study examined only a single treatment of TENS. Whether longer duration or repeated TENS applications will provide more effective and sustained pain management in fibromyalgia patients remains to be	Table data do not suggest efficacy but graphic data do for pain. Crossover design data suggest TENS may provide short term benefit for FM patients with one treatment but no ongoing on longer follow up.

			NIH R34 AR060378. No mention of COI					(p<0.05) or no TENS (5.0 ± 0.4)(p<0.05)	determined, ideally in a large-scale clinical trial. TENS is certainly not a 'cure' for fibromyalgia, but should be considered as an additional non-pharmacological treatment option in an existing treatment plan."	
Löfgren M 2009 (5.0)	Fibromyalgia	RCT crossover study	This study was supported by the Swedish Rheumatism Association, the Department of Rehabilitation Medicine, Danderyd University Hospital and the Division of Rehabilitation Medicine, Karolinska Institutet, Department of Clinical Sciences, Danderyd	N= 32 female patients with FM	Mean age: 41.5 years	3 weeks of TENS (*n* = 16) Vs. superficial warmth stimulation (*n* = 16)	At baseline, at end of 3 weeks of treatment	There was no difference in level of pain relief when comparing the 2 treatment modes. Median pain intensity in patients using warmth therapy decreased from 77.5 on the numerical rating scale before treatment to 62.5 after treatment and in patients using transcutaneous electrical nerve stimulation from 80 to 62.5. Ten patients reported a reduction of 20 units or more on the numerical rating scale after warmth therapy, as did 10 after transcutaneous electrical nerve stimulation. Seventeen of 32 patients preferred warmth therapy and 10 preferred transcutaneous electrical nerve stimulation.	"In conclusion, sensory stimulation consisting of superficial warmth or TENS stimulation yielded comparable temporary reduction of pain in patients with FM. Both procedures may be self-administered, are safe and inexpensive, and may be combined with other FM treatment"	Data suggest comparable efficacy between groups pain relief was temporary

			Hospital, Stockholm, Sweden.							
Lauretti G 2013 (4.0)	Fibromyalgia	RCT	No mention of COI or sponsorship	N= 36 patients	Mean age: 32 years; (34 females, 2 males)	Placebo group (PG) (n=10) vs. Single active TENS device group (STG) (n=13) vs Double active TENS device group (DTG) (n=13)	1st through 7th day of study	The evaluation within groups revealed that patients from DPG refereed no pain relief when compared to their previous VAS pain score (8 cm, p>0.05), while patients from the STG refereed improvement of 2.5 cm in the pain VAS (previous 8.5 cm compared to 6 cm after treatment) (p<0.05), and the DPG refereed daily maintained reduction of 4 cm in the VAS pain (previous 8.5–4.3 cm) (p<0.02).	"In conclusion, while the application of one active TENS device at either the lower back or cervical area improved pain relief in patients suffering from fibromyalgia pain, the pain and fatigue were further improved when two active devices were simultaneously applied at the low back and cervical area, reflecting its usefulness as adjuvant for fibromyalgia pain."	Data suggest pain and fatigue improvement from simultaneous use of two TENS devices.

Evidence for Hyperbaric Oxygen

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Efrati 2015 (6.0)	Hyperbaric Oxygen Therapy (HBOT)	Active control, crossover clinical trial	Supported by the research fund of Assaf-Harofeh Medical Center. No COI.	N = 60 patients with Fibromyalgia	Mean age of Treated Group 50.4±10.9 Crossover Group 48.1±11.1 Sex(M:F) 0:60	Treated Group (N=24) were evaluated at baseline and after HBOT treatment. HBOT treatment was comprised of 40 sessions, 5x/week for 90mins. Crossover group: (N=26) was evaluated at baseline, after a control period (2 months), and after HBOT treatment.	Approximately 1-4 weeks after HBOT.	HBOT significantly lowered Tender Points in patients. Dolorimeter threshold score following HBOT. Treated group (mean change 1.11±0.79 ($p < 0.001$)) Crossover group after HBOT (mean change 1.29±0.76, ($p < 0.001$)). FIQ score significantly improved following HBOT in the treated group (mean change 1.31±0.99, ($p < 0.001$)) and in the crossover group after HBOT (mean change 1.02±0.92, ($p = 0.05$)). SCL-90 score significantly improved following HBOT in the treated group (mean change 1.10±0.79, ($p < 0.01$)) and in the crossover group after HBOT (mean change 1.29±0.76, ($p = 0.05$)). The SF-36 score significantly improved following HBOT in the treated group (mean change 0.34±0.33, ($p < 0.01$)) and in the crossover group after HBOT (mean change 0.23±0.39, $p = 0.05$))	"This study provides evidence that HBOT can improve quality of life and wellbeing of many FMS patients."	Crossover design. Data suggest hyperbaric oxygen therapy may modify brain activity related to pain in fibromyalgia patients. No sham hyperbaric oxygen therapy.

Evidence for Reiki

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Assefi 2008 [6.0]	Reiki	RCT	Sponsored by grant from the National Center for Complementary and Alternative Medicine, National Institutes of Health. No COI.	N = 100 with fibromyalgia (FM).	Mean age 49 years, 92 females and 8 males.	Group 1, direct contact treatment delivered by a Reiki (N = 25) vs Group 2, distant Reiki administered by a master who sat ~2 feet away (N = 25) vs Group 3, sham direct contact Reiki at (N = 25) vs Group 4, actors sat ~2 feet away from participants and mimicked the "sending" position of distant Reiki (N = 25).	8-weeks	No treatment factor main effects were significant for any outcome: VAS pain / fatigue / sleep quality / and well-being for Reiki master vs. Direct touch; p = 0.31 / 0.31 / 0.52 /and 0.61 vs 0.52 / 0.45 / 0.78 /and 0.51	"Neither Reiki nor touch improved the symptoms of fibromyalgia."	Data suggest comparable (in) efficacy between all groups. Reiki is not superior to other intervention for FM pain.

Evidence for Qigong

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Stephens 2008 (5.5)	Aerobic Exercise	RCT	Sponsored by the Hospital for Sick Children Foundation and by a complementary	N=30 children 8-18 and were diagnosed with fibromyalgia.	8 males, 22 females; Mean age in qigong group is 12.9±2.7 and aerobics	Qigong Group (N=16) participants did 3 weekly sessions (1 supervised, 2 unsupervised) qigong (Low impact posture	Follow up at baseline and 12 weeks.	Childhood Health assessment questionnaire (C-HAQ) aerobic group was superior to qigong group in physical function scores and in severity of illness and pain: (F [1, 22] = 4.4, p=0.05)	"The results of this randomized controlled pilot trial of a 12 week exercise intervention suggest that it is feasible and safe for children with FM to participate	Small sample pilot study. Sample aged 8-18 mean age =14. Data suggest improved physical function, less fatigue and

					group 13.6±1.8.	exercises) workouts for 12 weeks. vs Aerobics group (N=14) participated in 30 minutes of boxing/cardio-dance movements with a goal of achieving 70% max HR.		and (F [1, 21] = 5.32, p=0.03) and (F [1, 21] = 9.75 p=0.005), respectively. PedQL fatigue section aerobics group improved more (F [1, 22] = 7.96, p=0.01). Overall Quality of Life (QoL) aerobics group had superior improvement (F [1, 22] = 6.50, p=0.01).	in a moderate-intensity aerobic exercise program. Exploratory analyses suggest that aerobic exercise may be beneficial in reducing plain, improving QOL, decreasing FM symptoms of fatigue, and increasing physical function in children with FM.	better QoL in aerobics group.

Evidence for Biofeedback

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
van Santen 2002	6.0	Study reviewed in Exercise Section.				
Babu 2007 RCT	5.5	N = 30 with FM (ACR criteria used)	45-minute sessions of biofeedback vs. sham biofeedback	Both groups showed significant decreases in VAS scores (baseline/post): biofeedback (7.5/3) vs. sham (8.1/5). Decrease in tender points greater in biofeedback group (15/6) vs. (14/10).	"Biofeedback as a treatment modality reduces pain in patients with FMS, along with improvements in FIQ, SMWT [six minute walk test] and the number of tender points."	Sham treatment consisted of use of a biofeedback machine that was altered to not give true feedback; however, it is not clear how this fully blinded the professional.

Evidence for Relaxation and Meditation Training

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Haanen 1991	6.5	Study reviewed in Exercise Section.				
Buckelew 1998 RCT	5.5	N = 119 patients with FM (Yunus criteria used)	Biofeedback/ relaxation treatment vs. exercise training vs. combined treatment vs. an educational/	Minutes per mile walked (baseline/post-treatment/18 months/24 months): exercise group (17.1/16.4/16.6/16.8) vs. combination group (18.3/17.2/15.9/15.9). Tender point indices (baseline/post-treatment/3 month/1 year/2 year): biofeedback	"This study demonstrates that these 3 treatment interventions result in improved self-efficacy for physical function which was best maintained by the combination group."	Inexplicably less than half of subjects measured at 18 and 24 months in combination group when dropout rates were elsewhere claimed to be under 15% in those intervals. Attention control group

			attention control group.	(1.5/1.2/1.3/1.6/1.4) vs. exercise (1.6/1.3/1.4/1.5/1.5) vs. combination (1.1/1.0/ 1.1/1.0/1.1) vs. attention controls (1.2/1.4/1.4/1.6/ 1.4). VAS scores: biofeedback (5.8/3.6/5.2/5.9/5.2) vs. exercise (6.3/4.6/5.4/5.4/5.5) vs. combination (5.0/4.6/ 3.2/5.0/5.8) vs. attention controls (5.9/5.3/5.8/5.9/5.4).		somewhat less likely to view their treatment arm as credible for treatment of fibromyalgia. Combination groups had lower baseline tender point scores.
Fors 2002	5.0	Study reviewed in Anti-depressants Section.					
Wigers 1996	4.5	Study reviewed in Exercise Section.					
Sephton 2007 RCT	4.5	N = 91 females with FM (ACR criteria used)	8-week trial of 2.5 hour sessions of Mindfulness-Based Stress Reduction vs. wait-listed controls	Most (82%) attended at least 50% of sessions. Beck Depression Inventory scores (baseline/post treatment/2-months): treatment (15.7±7.1/ 12.4±7.4/13.3±7.5) vs. controls (14.7±6.9/ 15.1±8.1/14.8±8.1).	"Meditation-based intervention alleviated depressive symptoms among patients with fibromyalgia."	Use of wait-listed controls biases in favor of intervention.
Martin 1996	4.0	Study reviewed in Exercise section.					

Injection Therapies

Evidence for Ganglion Blocks

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:

Scudds 1994 (6.5)	Ganglion Blocks	RCT	Sponsored by Atsra Pharam (Canada). No mention of COI.	N = 61 patients diagnosed with fibromyalgia or chronic pain syndromes using the 1990 American College of Rheumatology criterion.	8 males, 53 females; Mean age of 45±9.2.	Lidocaine (LID) (N =31) Received topical 4% concentrated lidocaine inserted within the mucous membranes. vs Placebo (PLAC) (N =30) received sterile water in substitute of lidocaine.	Baseline, post-treatment (3 weeks), and 4 weeks after posttreatment	Pain ratings did not fluctuate significantly in both groups at all assessments. No difference in acetaminophen pills taken during the study period, LID; M=75 pills. PLAC; M=69 pills. LID and PLAC showed similar results for all major variables in the study.	"In conclusion, the results of this study do not support the use of 4% Lidocaine in the topical blockade of the spheno-palatine ganglion for the treatment of chronic muscle pain syndromes. Further, well controlled clinical trials are needed to show if this technique has any utility in the treatment of other types of chronic pain.	Data suggest lack of efficacy between 4% lidocaine and placebo for treatment of chronic muscle pain.
Janzen 1997 (4.5)	Sphenopalatine Blocks	RCT	Funded by a grant from ASTRA Pharma Inc., Canada. No mention of COI.	N = 61	Mean age is 45 years. 8 males, 53 females.	Placebo (N = 30) vs. Lidocaine (N = 31).	3 weeks	No significant differences were found between the two groups at any time (P>0.05). Pain over time (P>0.05) and interaction (P>0.05). Pain before and pain after the sphenopalatine block showed no significance (P>0.05).	"No definite criteria existed to indicate that a block had actually occurred even though the pledgets were placed under direct vision in the appropriate location."	Data suggest lack of efficacy

Evidence for Ketamine Infusions

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Noppers I, 2011 (6.5)	Ketamine vs. Midazolam	RCT	Sponsored by the TREND (Trauma Related Neuronal Dysfunction) organization. No COI.	N=24 patients with fibromyalgia.	The mean age of the ketamine group is 39.1 years. 1 male, 11 females. The mean age of the midazolam group is 45.2 years. 0 males, 12 females.	Ketamine Group (n=12) – Patients received a 30 minute intravenous infusion with S (+)-ketamine (total dose 0.5 mg/kg). Vs. Midazolam Group (n=12) – Patients received a 30 minute intravenous infusion with midazolam, the active placebo, and (5 mg).	Single treatment followed by 8 week follow up.	The FIQ scores at baseline were 52 ± 4 and 50 ± 3 in S-ketamine and midazolam groups, respectively. No time (P = 0.07), group (P = 0.98) or interaction (P = 0.80) effects were observed in weeks 1–8 following treatment.	"In summary, we reject the hypothesis that a short-term infusion of relatively high-dose S-ketamine treatment produces long-term pain relief in fibromyalgia patients."	Data suggests each of short or long term efficacy.

Evidence of Lidocaine Infusions

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:		Follow-up:	Results:	Conclusion:	Comments:
Giraldes, A 2016 (Score = 5.5)	Fibromyalgia	RCT	Sponsorship by grant rom São Paulo Research Foundation. No mention of COI.	N = 42 patients with FM	40 females, 2 males; Mean age 44.7	Group 1 patients received 240 mg of lidocaine in 125 mL of saline Solution (N = 21) vs group 2 patients received 125 mL of saline, both once a week for 4 weeks (T1, T2, T3 and T4). (N = 21) All patients received amitriptyline.	8 weeks	Pain intensity; Lidocaine vs Saline T0 6.1 ± 1.3/7.2 ± 1.3 (p = 0.090) T2 4.6 ± 1.6/6.1 ± 1.7 (p = 0.010) T8 3.9 ± 2.8/2.7 ± 2.9 (p = 0.199)	"The combination of 240 mg of intravenous lidocaine (once a week for 4 weeks) with 25 mg of amitriptyline for 8 weeks had no meaningful impact in fibromyalgia patients."	Data suggest comparable (in) efficacy between groups from pain intensity in FM patients at 8 weeks but better at 2 weeks.
Vlainich, R 2010 (Score = 5.0)	Fibromyalgia	RCT	No mention of sponsorship or COI.	N = 30 with FM	30 females; mean age 42.8	All patients received 25 mg Amitriptyline. Group 1 received 125 mL of .09% saline. (N = 15) vs Group 2 received 240 mg lidocaine in 125 mL of	4 weeks	Sleep disorders G1 (T0: 15 and T4: 2) and group 2 (T0: 14 and T4: 3) Paresthesia in G1 (T0: 12 and T4: 5) and G2 (T0: 14 and T4: 3) Headache in G1 (T0: 8 and T4: 1) and G2 (T0: 9 and T4: 2) Reduction of fatigue in G1 (T0: 15 and T4: 10 patients) and G2 (T0: 15 and T4: 9	"The combination of 240 mg intravenous lidocaine (once a week) and 25 mg amitriptyline for 4 weeks did not modify pain intensity or manifestations in patients with fibromyalgia compared with amitriptyline alone."	Data suggest comparable (in) efficacy between groups.

						.09% saline once a week for 4 weeks. (N = 15)		patients)		

Evidence for C2 Nerve Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Plazier, M 2015 (Score = 4.5)	Fibromyalgia	RCT	No mention of sponsorship or COI.	25 patients with FM.	No mention of sex or age.	Study arm A 1 mA at a pulse width of 300 µs over the implanted electrode vs Study arm B sub sensory threshold stimulation for two weeks	6 months	FIQ baseline 65.54, 24 weeks 43.50 (p = <.001). PVAQ base line 41.36, 24 weeks 31.72 (p = .002) PCS base line 21.24, 24 weeks 10.80 (p < .001)	"Subcutaneous C2 nerve field stimulation seems to offer a safe and effective treatment option for selected medically intractable patients with fibromyalgia."	More than 50% of study population reported and adverse outcome. 6/34 adverse effect resulted in an additional surgery. Data suggest at 6 months there was overall improvement in QOL

Evidence for Self-Management

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hamnes, 2012 (5.0)	Fibromyalgia	RCT	Funded by the Hospital for Rheumatic Diseases, Lillehammer, Norway.	N = 150 patients with fibromyalgia	Mean age: SMP group 45.4, Control group 49.7. Sex(M:F) 6:141	The SMP group (N=75) received one week of self-management program based on enhancing self-efficacy and coping with the disease in everyday life. Control group (N=72) was put on a wait-listing and received one week of SMP after 8 months or more.	Three weeks before SMP and 3 weeks after SMP.	There were no significant differences seen in psychological distress (GHQ-20) 3 weeks after SMP (p=0.55) between SMP group and control group. Significant differences were found between SMP group vs Control group in EC-17 from baseline (57.5 vs 54.3) to post treatment (63.0 vs 56.8 (p = 0.016)). No significant differences in self-efficacy between both groups 3 weeks following intervention.	"This study shows that in patients with FM the SMP had no effect on psychological distress, functional and symptomatic consequences and self-efficacy, except for a small short term effect on skills and behavior that are important for managing and participating in health care (EC-17)."	Waitlist control bias. Data suggest SMP had little if any effect on psychological distress, function and symptomatic consequences and self-efficacy in FM patients. There was a difference at 3 weeks by the treatment group in the EC-17.
Cedraschi, 2003 (5.0)	Self-management	RCT	Supported by Swiss National Foundation for Research, No mention of COI.	N = 164 patients with fibromyalgia.	Mean age: Treatment group 48.9, Control group 49.8. Sex(M:F) 12:152	Treatment group (N=84) (TG) received a 12-session programme meeting 2x/wk for 6 weeks. The programme included the	6 months	The treatment group in comparison to the WL group (Mean difference from baseline to follow up TG vs WL) had significant improvement in	"A 6 week self-management based programme of pool exercises and education can improve the quality of life of patients with FM and their	Waitlist control bias. Data suggest a 6 week self-managed program of pool exercise and education can improve quality

						promotion of self-management and exercise sessions. The waitlist group (WL) (N=80) was offered the programme after the 6 month follow up.		PGWB (anxiety) (-1.6 vs 0.5 (p=0.011)), vitality (-0.9 vs 0.2 (p=0.013)), and total scores (-5.2 vs 0.2 (p=0.007)). TG in comparison to WL also had significant improvements in total FIQ score (0.6 vs 0.1 (p=0.02)), pain (0.2 vs -0.6 (p=0.02)), fatigue (1.0 vs -0.3 (p=0.003)), and depression (0.9 vs -0.2 (p=0.03)).	satisfaction with treatment."	of life and treatment satisfaction in fibromyalgia patients.
Rooks DS, 2007 (4.5)	Exercise	RCT	Sponsored by an Arthritis Foundation Investigator Award (Dr Rooks) and National Institutes of Health grants K23 AR48305 (Dr Rooks), RO3 AR047398 (Dr Rooks), K24 AR02123 (Dr Katz), P60 AR47782 (Dr Iversen and and Katz), and RR01032 (Dr Gautan). No COI.	N = 207 patients with fibromyalgia.	The mean age of the AE group is 48 years. 0 males, 35 females. The mean age of the ST group is 50 years. 0 males, 35 females. The mean age of the FSHC group is 51 years. 0 males, 27 females. The mean age of the ST-FSHC group is 50	AE (n=35) – Aerobic and Flexibility exercise. Vs. ST (n=35) – Strength training, aerobic, and flexibility exercise. Vs. FSHC (n=27) – Fibromyalgia Self-Help Course.	6 months.	The Self-efficacy scale for pain reported difference between pre and post intervention the following scores: AE – 9.8 (p<0.01 for within group changes) (p<0.05 between-group differences of change compared to education group). ST – 2.5 (p<0.05 between-group differences of change compared to education group). FSHC - -11.0 (p<0.001 for within group changes). ST-FSHC – 7.6 (p<0.05	"Our findings suggest that appropriate exercise and patient education be included in the treatment of fibromyalgia."	Data suggests a combination of self-management education with exercise is the best treatment of fibromyalgia. Progressive walking and flexibility with or without strength training improves physical, emotional, and social functions.

					years. 0 males, 38 females.	ST-FSHC (n=38) – Combination of strength training, aerobic, and flexibility exercise with the Fibromyalgia Self-Help Course.		for within-group changes) (p<0.05 between-group differences of change compared to education group).		

Evidence for Self-Awareness

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hsu 2010 (6.5)	Self-Awareness	RCT	Supported in part by the Scott F. Nadler, DO, Research Grant (Physiatric Association of Spine, Sports, and Occupational Rehabilitation); and by grant numbers U020912 (Michigan Institute of Clinical and Health Research); T32-HD007422, K12HD001097 (NICHD/NIH); AR049059, (NIAMS/	N = 45	45 females, 0 males. Mean age is 50.1 years.	ASA Group (N = 24) vs. Control Group (N = 21)	6 months	At 6-months, 45.8% treatment participants had at least 30% pain reduction, and 20.8% had at least 50% pain reduction. They were significant greater than the o% of controls (p = 0.001 and p = 0.02). There was also higher reported physical function (p < 0.001).	"An affective self-awareness intervention resulted in a sustained reduction in pain and improvement in physical functioning in a sample of women with fibromyalgia compared to wait-listed controls."	Waitlist control bias, Contact time bias. Data suggest interventional group (ASA) had reported less pain severity and better physical function.

			NIH); and DAMD 17-00-2-0018 (Department of Defense). One potential conflict of Interest.							

Evidence for Attention Modification

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Carleton, 2011 (6.0)	Attention modification	RCT	No mention of sponsorship or COI.	N = 21 patients with fibromyalgia	Mean age: 52.5 Sex(M:F) 0:15	The attention modification paradigm (AMP) group (N=9) completed two 15min AMP sessions a week for 4 weeks. The attention control condition (ACC) group (N=8) received identical intervention as the AMP group but the attention of the participant was not implicitly directed away from threat words.	4 weeks	In the AMP group, there was a significant reduction in ASI-3 (r^2= .39, (p <0.05)). 44% of the AMP group reported clinically significant changes in VAS scores in comparison to only 17% of the ACC group.	"These preliminary results offer a new promising new avenue for treating chronic musculoskeletal pain that warrants additional research."	Small sample. Data suggest AMP may benefit patients with fibromyalgia.

Evidence for Guided Imagery

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Van Ittersum 2014 (6.0)	Guided Imagery	RCT	Funded by the Covenant between	N=114 patients diagnosed	8 males, 106 females;	Pain Neuroscience Education (PNE)	Baseline 1, Baseline 2 (3 weeks	There were no notable significant differences	"Taking the study limitations and	Data suggests lack of efficacy.

			University of Groningen and Hanz University of Applied science, Netherlands. No mention of COI.	with Fibromyalgia (FM) by the American College of Rheumatology criteria.	Mean age of 46.5±9.3.	(N=53) received educational booklet about pain. vs Relaxation Education (RE) (N=52) received written instruction on how to do relaxation exercises.	later), 6 months.	between the groups of patients. Both groups did not show significant improvement and were comparable to one another. However, both patient groups thought treatments were positive.	literature findings into account, it is concluded that written pain neuroscience education alone is not effective for changing the impact of the illness on daily life, pain catastrophizing, or illness perceptions in patients with FM. One-on-one sessions are required for explaining pain neuroscience to patients with FM."	
Vervaik 2014 (4.5)	Guided Imagery	RCT	Funded by Fonds NutsOhra, Amersterdam, Netherlands. No mention of COI.	(N=65) patients with Fibromyalgia.	1 male, 64 females; mean age of 47.4±11.4.	Guided Imagery (GI) group (N=32) received 2 1.5 hr. sessions on Guided Imagery instruction and exercises to do. vs Attention Control (N=33) received only 2, 1.5hr sessions, that were discussion based.	Follow up at baseline, 4 weeks, and 10 weeks.	Both groups showed no change in pain intensity, functional status, or Self-Efficacy for managing pain over time. There was no difference between groups.	"No effects of guided imagery could be established. Explanations for the diverging results between studies might be found in the content of the exercises, length of the intervention period, and background of participants."	Data suggest a lack of efficacy.

Evidence for Virtual Reality

Bieber 2006 (4.0)	Virtual Reality	RCT	Study supported by a grant from the German Federal Ministry of Health. No mention of COI.	N=67 patients diagnosed with Fibromyalgia (FM) by the American College of Rheumatology criteria.	4 males, 63 females; Mean age for SDM group is 51.5±9.5, info group is 50.6±9.6.	Shared Decision making (SDM) group (N=34) physicians received 12, 1.5 hr., sessions focusing on building rapport with patients. vs. Computer-based visualized information (Info) (N=33) Patients received guidance on symptoms, treatment options, etc. from a computer based developed software.	Baseline, 3 month, and 1 year follow up, secondary analysis.	Patient appraisal of interaction using FAPI, SDM was better using ANCOVA analysis at all follow ups, (T1, T2, and T3): (T1: t = 3.02, d.f. = 61, p < 0.01, effect size = 0.74; T2: t = 2.09, d.f. = 61, p < 0.05, effect size = 0.51; T3: t = 3.51, d.f. = 61, p < 0.001, effect size = 0.89). Coping, SDM vs Info: 64% improvement vs 28% improvement.	"Treatment in accordance with SDM principles can lead to an improved physician–patient relationship from the patients' and from the doctors' perspective. An SDM intervention has no influence on health related measures, but it can ameliorate coping in FMS patients and encourage them to adopt more active treatment plans."	Data suggest that coping improved in shared decision making group but healthy outcomes were comparable between groups.

Evidence for Acceptance and Commitment Training

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Larsson A 2015 (6.0)	Fibromyalgia	RCT	No COI. The study was supported by the Swedish Rheumatism Association, the Swedish Research Council, the Health and Medical Care Executive Board of Västra Götaland Region, ALF-LUA at Sahlgrenska University Hospital, Stockholm County Council (ALF), The Norrbacka-Eugenia foundation, and Gothenburg Center for Person Centered Care (GPCC)	N=130 women with fibromyalgia	Mean age: 51.5 years; all females.	Resistance exercise (experimental) (n = 67) Vs. Relaxation therapy (control) (n = 63)	13-18 months	Significant improvements were found for isometric knee-extension force (p = 0.010), health status (p = 0.038), current pain intensity (p = 0.033), 6MWT (p = 0.003), isometric elbow flexion force (p = 0.02), pain disability (p = 0.005), and pain acceptance (p = 0.043) in the resistance exercise group (n = 56) when compared to the control group (n = 49). PGIC differed significantly (p = 0.001) in favor of the resistance exercise group at post-treatment examinations. No significant differences between the resistance exercise group and the active control group were found regarding	"Person-centered progressive resistance exercise was shown to be a feasible mode of exercise for women with FM, improving muscle function, health status, current pain intensity, pain management and participation in activities of daily life. At long-term follow up the effects had declined to baseline levels, implying that a longer period of guidance and support is recommended to increase the possibilities of maintaining regular exercise habits."	Data suggest person centered progressive resistance exercise improved fatigue and muscle strength in FM women and pain intensity immediately after exercise. Data suggest significant short term improvement from progressive resistance exercise in terms of knee extension force elbow flexion force pain disability, pain acceptance and pain intensity compared to controls but at 13-18 month there were no significant differences between groups.

								change in self-reported questionnaires from baseline to 13–18 months		
Wicksell 2012 [4.5]	Acceptance and Commitment Therapy	RCT	Sponsored by the Swedish Research Council, Project No. K2009-53X-21070-01-3, the Stockholm County Council, and the Swedish Rheumatism Association. No COI.	N = 40 with fibromyalgia (FM).	Average age 45.1 years, 40 females.	Acceptance and commitment therapy or ACT defined as the ability to notice and accept interfering thoughts, emotions and bodily sensations without acting on them (N = 23) vs Waitlist group, treatment offered after follow-up assessments (N = 17).	3-months	ACT vs control, Condition, time x interaction: F (1,67) = 16.59, p < 0.001. Effect size (d); medium to large between-group effects at post (0.75) vs follow-up (0.73).	"The results correspond with previous studies on ACT for chronic pain and suggest the utility of ACT for FM as well as the role of psychological inflexibility as a mediator of improvement."	Data suggest ACT may benefit FM for chronic pain and improving psychological inflexibility.
Wetherell 2011 [4.5]	Acceptance and Commitment Therapy	RCT	Sponsored by the Grant F4306I from VA Rehabilitation Research and Development Service (J.L.W.). No COI.	N = 114 with chronic, nonmalignant painof any type for at least 6 months, with pain severity and interference ratings of at least 5/10 on a numerical rating scale.	Aged 18-89 years,	ACT group, eight 90-min weekly (N = 57) vs CBT intervention, eight 90-min weekly, using pain monitoring, pacing, increasing pleasant activities, progressive muscle	4-6 weeks	Average ACT group scores pre-treatment period: effect of pain interference / depression / and pain-related anxiety: p = 0.02 / p = 0.004 / and p < 0.001. No significance between post and follow-up. CBT group: pain interference /	"These findings suggest that ACT is an effective and acceptable adjunct intervention for patients with chronic pain."	Data suggest comparable efficacy. Data suggest participants thought CBT more credible but ACT was preferred.

						relaxation, thought challenging etc. (N = 57).		depression / pain related anxiety: p < 0.001 / p < 0.001 / and p = 0.004.		
Currie, 2000 4.0	Cognitive Behavioral Therapy	RCT	Sponsorship grants from The Rehabilitation Centre Research Development Fund and the Physical Medicine Research Foundation, as well as by a doctoral fellowship from the National Health Research Development Program.	N = 60 patients with insomnia secondary to chronic pain. Mostly LBP.	Mean age 45 years: 27 males, 33 females.	Cognitive behavioral therapy (CBT) 7 weeks of group intervention promoting good sleep habits, teaching relaxation skills, and negative thoughts about sleep. vs self-monitoring/waiting-list control condition.	3 months	Sleep onset latencies for CBT participants at post-treatment reduced by an average of 26.6 min from baseline values (p < 0.001) remained at follow-up. CBT participants had lower sleep onset latencies than did WLC participants at both post-treatment (p < 0.005) and follow up (p < 0.025) Over time change in the CBT group (p < 0.001) WLC group (p < 1)	"The results of the present study provide the first evidence from a randomized controlled trial that CBT can help to relieve insomnia secondary to chronic pain. As hypothesized, participants in the CBT condition showed significant improvements in most sleep parameters. Self-report measures of sleep onset latency, sleep efficiency, wake time after sleep onset, and sleep quality showed the greatest change with treatment."	Data suggest short term use of CBT improved self-reported sleep measures associated with chronic pain at 3mo.

Evidence for Psychoeducational Treatment

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Oosterwijck 2013 (6.0)	Fibromyalgia	RCT	Author Oosterwijck was sponsored by a grant from the research council of the Vrije Universiteit Brussel. Author Meeus is a postdoctoral research fellow of the Research Foundation Flanders (FWO).	N = 30 patients who met the 1990 American College of Rheumatology fibromyalgia criteria	26 female, 4 male. Mean age experimental group 45.8 years, control group 45.9 years	One-on-one educational sessions about neurophysiology of Pain (experimental) (n = 15) vs One-on-one educational sessions about activity self-management techniques (control) (n = 15). Each participant received two educational sessions: first being through PowerPoint presentation, second being a telephone call.	2 weeks, then again at 3 months	Mean neurophysiology of pain test score at baseline, post intervention, 14 day follow-up and 3 month follow-up, respectively: experimental group 5.5, 10.9, 11.4, 11.3, control group 5.9, 7.1, 6.8, 7.2, within-group comparison ($F = 10.3$, $P < 0.001$), Cohen's *d* ES -1.97.	"These results suggest that FM patients are able to understand and remember the complex material about pain physiology. Pain physiology education seems to be a useful component in the treatment of FM patients as it improves health status and endogenous pain inhibition in the long term."	Data suggest pain education may be useful as a tool for treating FM patients.
Luciano, J 2011 (Score = 6.0)	Fibromyalgia	RCT	Supported by a grant from the "Age`ncia d'Avaluacio´ de Tecnologia i Recerca Me`diques. No mention of COI.	216 patients with FM	211 females, 5 males; mean age 55.3	Intervention group, received 5 sessions of education and 4 sessions of autogenic reaction. (N = 108) vs Usual care (N = 108)	12 months	Intervention vs Control functional status (FIQtot) than the control group [F(1, 213)=39.72, (p = 0.001), 95% confidence interval (CI): 7.20-13.76], and less physical impairment [F(1, 213)=19.94,	"A 2-month psychoeducational intervention improves the functional status of FM patients to a greater extent than usual care, at least in the short-term. The social desirability bias did not explain the reported	Data suggest psychoeducational group improved FM symptoms better than usual care group.

								(p = 0.001), 95% CI: 0.66-1.70], days not feeling well [F(1, 213)=19.62, (p = 0.001), 95% CI: 0.97-2.53], pain [F(1, 213)=28.52, (p = 0.001), 95% CI: 0.86-1.86], general fatigue [F(1, 213)=8.21, (p = 0.005), 95% CI: 0.24-1.30], morning fatigue [F(1, 213)=10.77, P=0.001, (p =0.05), 95% CI: 0.36-1.45], stiffness [F(1, 213)=7.35, p= 0.007, (p =0.03), 95% CI: 0.23-1.47], anxiety [F(1, 213)=19.41, P=0.001, (p 2 =0.08, 95% CI: 0.79-2.06], and depression [F(1, 213)=21.44, (P=0.001), (p=0.09), 95% CI: 0.93-2.31].	outcomes. Trait anxiety was associated with response to treatment."	
Ang DC, 2013 (5.0)	Motivational Interviewing	RCT	Sponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. No mention of COI.	N=216 patients with Fibromyalgia.	The mean age of the motivational interviewing group is 46 years. 4 males, 103 females. The mean age of the	Motivational Interviewing (MI) (n=107) – received six telephone-delivered exercise-based MI sessions for a 12 week period. Vs.	Patients assessed at baseline, 12 weeks, 3 month follow up, and 6 month follow up.	The change is FIQ-physical impairment at 6 month follow up is -1.7 (p<0.01) for MI intervention group and -1.4 (p<0.01) for the education control group. P=0.39 MI vs. EC. The percent of	"Despite a lack of benefits on long term outcome, MI appears to have short-term benefits with respect to self-report physical activity and clinical outcomes."	Data suggests some minor short term benefits but general lack of efficacy.

					education control group is 45.7 years.	Education control (EC) (n=109) - received an equal number of telephone contacts to control for time and therapist attention.		subjects with ≥ 30-minute increment of MPVA (CHAMPS) at 6 month follow up is 54% MI intervention group and 52% education group. P=0.89.		
Luciano, J 2013 (Score = 4.5)	Fibromyalgia	RCT	Supported by a grant from the "Catalan Agency for Health Information	216 patients with FM	211 females, 5 males; mean age 55.3	Intervention group, received 5 sessions of education and 4 sessions of autogenic reaction. (N = 108) vs Usual care (N = 108)	12 months	Intervention vs Control FIQ 48.04, 54.09 (p = 0.001) pain 6.82, 7.60 (p = 0.006)	"Our findings demonstrate the long-term clinical effectiveness of a psychoeducational treatment program for FM implemented at primary care level and cost-utility from a health care and societal perspective.	Data suggest long term efficacy and cost-utility of psychological intervention for FM patients.

Evidence for Written Pain Education and Disclosures

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Van Ittersum 2014 (6.0)	Guided Imagery/Virtual Reality	RCT	Funded by the Covenant between University of Groningen and Hanz University of Applied science, Netherlands. No mention of COI.	N=114 patients diagnosed with Fibromyalgia (FM) by the American College of Rheumatology criteria.	8 males, 106 females; Mean age of 46.5±9.3.	Pain Neuroscience Education (PNE) (N=53) received educational booklet about pain. vs Relaxation Education (RE) (N=52) received written	Baseline 1, Baseline 2 (3 weeks later), 6 months.	There were no notable significant differences between the groups of patients. Both groups did not show significant improvement and were comparable to one another. However, both patient groups	"Taking the study limitations and literature findings into account, it is concluded that written pain neuroscience education alone is not effective for changing the impact of the illness on daily life,	Data suggests lack of efficacy.

						instruction on how to do relaxation exercises.		thought treatments were positive.	pain catastrophizing, or illness perceptions in patients with FM. One-on-one sessions are required for explaining pain neuroscience to patients with FM."	

Evidence for Shared Decision Making

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Bieber 2006 (4.0)	Guided Imagery/Virtual Reality	RCT	Study supported by a grant from the German Federal Ministry of Health. No mention of COI.	N=67 patients diagnosed with Fibromyalgia (FM) by the American College of Rheumatology criteria.	4 males, 63 females; Mean age for SDM group is 51.5±9.5, info group is 50.6±9.6.	Shared Decision making (SDM) group (N=34) physicians received 12, 1.5 hr., sessions focusing on building rapport with patients. vs. Computer-based visualized information (Info) (N=33) Patients received guidance on symptoms, treatment options, etc. from a computer based developed software.	Baseline, 3 month, and 1 year follow up, secondary analysis.	Patient appraisal of interaction using FAPI, SDM was better using ANCOVA analysis at all follow ups, (T1, T2, and T3): (T1: $t = 3.02$, $d.f. = 61$, $p < 0.01$, effect size = 0.74; T2: $t = 2.09$, $d.f. = 61$, $p < 0.05$, effect size = 0.51; T3: $t = 3.51$, $d.f. = 61$, $p < 0.001$, effect size = 0.89). Coping, SDM vs Info: 64% improvement vs 28% improvement.	"Treatment in accordance with SDM principles can lead to an improved physician–patient relationship from the patients' and from the doctors' perspective. An SDM intervention has no influence on health related measures, but it can ameliorate coping in FMS patients and encourage them to adopt more active treatment plans."	Data suggest that coping improved in shared decision making group but healthy outcomes were comparable between groups.

Evidence for Behavioral Interventions

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Thieme 2007 RCT	4.5	N = 125 with FM using ACR criteria	Cognitive-behavioral treatment (CBT) vs. operant-behavioral treatment (OBT) vs. attention placebo. All 15 weekly 2-hour sessions.	At follow-up, 53.5% vs. 45.2% vs. 5% reported clinically meaningful improvements in pain intensity ratings. Significant improvements in physical impairments: 58.1% vs. 38.1% vs. 7.5%. Low physical impairment predicted significant decrease in pain intensity. Duration of pain, psychological factors and behavioral factors did not predict reductions in pain.	"Pretreatment patient characteristics are important predictors of treatment response and may serve as a basis for matching treatments to patient characteristics."	Dropout rate in the attention controls (50%) suggests it was not a credible control.

Prognosis

The prognosis for fibromyalgia is primarily if not entirely determined by compliance with progressive exercises, primarily aerobic and strengthening. Anti-depressants, cognitive behavioral therapy, fear avoidant belief training and some other interventions may assist.

Differential Diagnosis

The differential diagnosis of fibromyalgia includes:

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyalgia rheumatic
- Myositis
- Dermatomyositis
- Ankylosing Spondylitis
- Hypothyroidism
- Neuropathies
- Chronic fatigue syndrome
- Lyme Disease
- Somatization Disorders
- Guillian-Barre
- Hypothyroidism

Complications / Comorbidities

- Depression
- Anxiety
- Panic disorder
- Bipolar
- Childhood or adult physical abuse
- Childhood or adult sexual abuse
- Stress
- Psychological distress
- Familial mood disorder
- Catastrophization
- Advocagenesis
- Somatoform disorder
- Somatoform pain disorder
- Somatization
- Low vitamin D levels
- Chronic Hepatitis C infection
- Human T-cell lymphotropic virus type I infection
- HIV
- Autoimmune thyroid disease
- Epilepsy

- Hemochromatosis
- Fatigue
- Sleep disturbances
- Cognitive difficulties
- Alcohol
- Autoimmune disorders
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyalgia rheumatic
- Myositis
- Dermatomyositis
- Ankylosing Spondylitis
- Hypothyroidism
- Neuropathies
- Chronic fatigue syndrome
- Lyme Disease
- Somatization Disorders
- Guillian-Barre
- Hypothyroidism
- Irritable bowel syndrome
- Chronic headaches
- Temporomandibular joint disorders
- Orofacial pain
- Multiple chemical sensitivity

Follow-up Care

It is **Recommended (I)** that patients with work-related neuropathic pain should have a follow-up visit every 1 to 2 weeks initially by a new health care provider or while still out of work. Appointments should generally be time-contingent, i.e., scheduled as opposed to obtained secondary to changes in pain complaint. The initial appointments should focus on identify remediable causes of neuropathic pain and exposure elimination, if a neurotoxin is identified.

Initial visits should include an ongoing focus on function, obtaining more information from the patient, confirming that the history information is consistent, observing for injury/illness behaviors, confirming the diagnosis, and assessing the need for psychological referral and evaluation. The educational process of informing the patient about functional status and the need to engage in a functional rehabilitation program focusing on restorative exercises should be reinforced. These restorative exercise program components should be labeled the cornerstone of the medical management plan for the patient's pain. Other means of managing pain, including pharmaceuticals should be addressed. Initial visits for chronic pain should also include information to avoid bed rest, excessive rest or appliances. The provider should take care to answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery.

Subsequent follow-up is **Recommended (I)** to be less frequent, and tailored to the patient's needs. In cases where the patient is at work, fully functional and on minimal or steady-state maintenance NSAID medications, follow-up every 6 to 12 months is **Recommended (I)**. However, in the active rehabilitation

phase for patients with neuropathic pain, follow-ups weekly for as much as 2 or 3 months is **Recommended (I)** to also be conducted if there is need for physical therapy and occupational therapy to sustain a team-oriented focus on restoration and achievement of functional goals.

Psychological Services

Psychological and behavioral factors are key components of chronic nonmalignant pain conditions including fibromyalgia and are discussed in detail in the behavioral section of the Chronic Pain guideline.

Job Analysis

There is little reason to perform job analyses for patient with fibromyalgia as it tends to impair the recovery from the condition by externalizing the condition instead of focusing on progressive exercise.

Neuropathic Pain

Summary of Recommendations

The following summary table contains recommendations for evaluating and managing neuropathic pain from the Evidence-based Chronic Pain Panel. These recommendations are based on critically appraised higher quality research evidence or, when such evidence was unavailable or inconsistent, on expert consensus as required in ACOEM's Methodology. Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient – Recommended (Consensus-based), "I" Level
- Insufficient – No Recommendation (Consensus-based), "I" Level
- Insufficient – Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

Laboratory Tests for Peripheral Neuropathic Pain	Recommended, Evidence (C)
Occupational Neurotoxin Exposure Measurement(s)	Recommended, Evidence (C)
Antibodies to Confirm Specific Disorders	Strongly Recommended, Evidence (A)
ANSAR Testing for Diagnosing Chronic Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Non-specific Inflammatory Markers for Screening for Inflammatory Disorders	Recommended, Evidence (C)
Cytokine Tests for Diagnosing Chronic Neuropathic Pain	Not Recommended, Evidence (C)
Needle EMG and Nerve Conduction Study to Diagnose	Recommended, Insufficient Evidence (I)
Surface EMG for Diagnosing Chronic Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Functional MRIs for Diagnosing Chronic Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Local Anesthetic Injections for Diagnosing Chronic Neuropathic Pain	Recommended, Insufficient Evidence (I)
SPECT/PET for Diagnosing Chronic Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
FCEs for Chronic Neuropathic Pain	Recommended, Insufficient Evidence (I)
Bed Rest for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)

Aerobic Exercise for Neuropathic Pain	Recommended, Insufficient Evidence (I)
Strengthening Exercise for Neuropathic Pain	Recommended, Insufficient Evidence (I)
Aquatic Therapy for Neuropathic Pain	Recommended, Insufficient Evidence (I)
Physical or Occupational Therapy for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
NSAIDs for Chronic Neuropathic Pain	Recommended, Insufficient Evidence (I)
Acetaminophen for Neuropathic Pain	Recommended, Insufficient Evidence (I)
Tricyclic, Tetracyclic, and SNRI Anti-depressants for Neuropathic Pain	Moderately Recommended, Evidence (B)
Selective Serotonin Reuptake Inhibitors for Neuropathic Pain	Recommended, Evidence (C)
Antipsychotics for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Anti-convulsant Agents for Neuropathic Pain	Moderately Recommended, Evidence (B)
Anti-virals for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Homeopathy and Complementary Medicines for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Clonidine for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Dextromethorphan for Neuropathic Pain	Recommended, Evidence (C)
Muscle Relaxants for Acute Exacerbations of Neuropathic Pain	Recommended, Insufficient Evidence (I)
Magnesium	Not Recommended, Evidence (C)
Tumor Necrosis Factor-alpha Blockers for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Topical NSAIDs for Chronic Pain Where Target Tissue Superficially Located	No Recommendation, Insufficient Evidence (I)
Other Topical Creams (Ketamine, Amitriptyline and Combination Ketamine and Amitriptyline)	Moderately Not Recommended, Evidence (B)
Capsaicin Patches for Neuropathic Pain	Moderately Recommended, Evidence (B)
Lidocaine Patches for Neuropathic Pain	Moderately Recommended, Evidence (B)
Motor Cortex Stimulation for Neuropathic Pain	Not Recommended, Evidence (C)
Magnets and Magnetic Stimulation for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Taping and Kinesiotaping for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Self-application or Healthcare Provider Application of Cryotherapies for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Diathermy for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)

Ultrasound for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Provider-Based or Self-Application of Infrared Therapy for Neuropathic Pain	Not Recommended, Evidence (C)
Low-level Laser Therapy for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Manipulation for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Massage for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Mechanical Massage Devices for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Myofascial Release for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Acupuncture/Electroacupuncture for Neuropathic Pain	Not Recommended, Evidence (C)
Reflexology for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
High-voltage Galvanic Therapy for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
H-Wave® Device Stimulation for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Interferential Therapy for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Iontophoresis for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Microcurrent Electrical Stimulation for Neuropathic Pain	Not Recommended, Evidence (C)
PENS for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
TENS for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Repetitive Transcranial Magnetic Stimulation (rTMS) for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Sympathetic Electrotherapy	Not Recommended, Insufficient Evidence (I)
External Radiation for Sympathetic Blockade for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Corticosteroids for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Immunoglobulin for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Ketamine Infusion for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Intrapleural Bupivacaine Infusions for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Lidocaine Infusion for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Intravenous Phenytoin for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)
Intravenous Adenosine for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Monoclonal Antibody Injections for Neuropathic Pain	No Recommendation, Insufficient Evidence (I)

Dorsal Ganglion Destruction for Neuropathic Pain	Not Recommended, Insufficient Evidence (I)
Nerve Blocks for Neuropathic Pain	Recommended, Insufficient Evidence (I)
Botulinum Toxin A (BTX_A) for Neuropathic Pain	Recommended, Insufficient Evidence (I)
Surgical Decompression for Neuropathic Pain	Recommended, Insufficient Evidence (I)
Spinal Cord Stimulation for Neuropathic Pain No Recommendation	No Recommendation, Insufficient Evidence (I)
Intrathecal Drug Delivery Systems for Chronic Nonmalignant Pain Conditions	Not Recommended, Insufficient Evidence (I)

Related Terms

- Nerve pain
- Radicular pain
- Radiculitis
- Diabetic neuropathy
- Alcoholic peripheral neuropathy
- Central nerve pain
- Peripheral nerve pain
- Phantom limb pain
- Shingles

Overview

Neuropathic pain is pathophysiologic pain associated with a nerve and has been defined by the International Association for the Study of Pain (IASP) as “pain initiated or caused by a primary lesion or dysfunction of the nervous system”[945] It is generally categorized as central or peripheral. While radicular pain and chronic CRPS are also forms of neuropathic pain, they are usually discussed as separate entities, as are acute forms of neuropathic pain that can be addressed by specific interventions. It is important to note that many times, neuropathic pain is not able to be objectively demonstrated, although sometimes, objective findings are present.

Chronic neuropathic pain has a reported prevalence of 8.2-8.9% of adults [946]. It has been estimated that 26.4% of Type 2 diabetics have painful peripheral diabetic neuropathy [947]. The cumulative incidence of diabetic neuropathy in Type 1 diabetics has been estimated at 17-25%. Two-thirds of those using insulin had some form of neuropathy in one population-based study [948]. Post-stroke pain has been estimated to affect 30% of stroke patients [949]. Other disorders considered to be neuropathic include: channelopathies (e.g., familial episodic pain syndrome, inherited erythromelalgia), intracranial tumor, multiple sclerosis, peripheral nerve entrapment, trigeminal neuralgia, polyneuropathy (e.g., post-chemotherapy, alcoholic, HIV disease), postherpetic neuralgia, radiculopathy, some spinal cord injuries, syringomyelia, syrinx of the central canal in the brainstem or spinal cord, traumatic nerve injury (identifiable separate from the pain complaint, e.g. amputation).

Risk and Causation

A method for determination of work-relatedness is discussed in detail in the Work-Relatedness Guideline. A discussion of work-relatedness of radicular pain is discussed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines and thus also not duplicated here. Complex Regional Pain Syndrome is addressed in the CRPS Guideline section.

Central Neuropathic Pain

The most common causes of central neuropathic pain include: transient ischemic attacks (TIAs), cerebrovascular accidents/infarcts [949-955] [956-962], brain cancers and metastases especially to the brain [946, 963-966], spinal cord injury [967-970], multiple sclerosis [950, 971-978]; [979-982], and spinal cord injuries [950, 967-969, 983-985]. Post-stroke pain has been estimated to affect 30% of stroke patients [645]. As most of these are considered non-occupational conditions, most are not reviewed further. Causation of spinal cord injuries is based on the mechanism of the accident/injury and thus is not usually considered controversial.

Some lung cancers are particularly considered occupational due to significant occupational exposures (see Table 13). A determination of work-relatedness of a cancer metastatic to the brain is generally complex, and importantly includes elements of frequency, intensity and duration of the exposure. Measurements or at least estimates of occupational exposure (dose) are generally required, with industrial hygiene data being particularly important when available. For many, there are confounding exposures that may overwhelm an occupational exposure (e.g., smoking); yet for some such as significant asbestos exposure, epidemiological evidence provides assurance that a high occupational exposure likely contributed to the cancer [986-997][998].

Peripheral Neuropathic Pain

There are many causes of painful peripheral neuropathies.[999, 1000] Risk factors for peripheral neuropathic pain include increasing age, genetics/inherited neuropathies [1001-1004][1005-1007], diabetes mellitus [138-145], alcohol abuse [138, 146-148], rheumatological disorders [1008], other autoimmune disorders [1009, 1010], prior varicella infection (zoster) [1011-1016], HIV/AIDS [1017-1019], leprosy [1020, 1021], and chemotherapeutics [139, 1022-1024]. Diabetes mellitus is thought to be the most common population-based cause [946, 947][948]. Idiopathic cases are also common, estimated at 20-30% [138].

Occupational causes of peripheral neuropathies include exposures to n-hexane [1025-1033], acrylamide [1034-1036], arsenic [1037-1046], carbon disulfide [1047-1054] [1055-1057], lead [1058-1064], and mercury [1065-1067]. A determination of work-relatedness of a peripheral neuropathy is generally complex, and importantly includes elements of frequency, intensity and duration of the exposure. Measurements or at least estimates of occupational exposure (dose) are generally required, with industrial hygiene data being particularly important when available.

Infrequently, trauma to a peripheral nerve may also cause peripheral neuropathic pain. Peripheral entrapment neuropathies may be occupational depending on the job's physical factors (see Hand, Wrist Forearm Guideline). Post-surgical trauma is a reported cause [963, 1068-1070], and the work-relatedness

of the post-surgical neuropathy would depend on the cause of the underlying condition requiring surgery. Paramalignant peripheral neuropathies also occasionally occur.

Table 13. Group 1 IARC carcinogens with sufficient evidence of causing lung cancer in humans and primary type of exposure

Agent	Primary Exposure Type
Ionizing radiation-all types	
• Alpha-particle emitters	E,O
○ Radon-222 and its decay products	E,O
○ Plutonium-239	O
• X-radiation, gamma-radiation	E,O
Chemicals and mixtures	
• Bis(chloromethyl)ether; chloromethyl methyl ether	O
• Coal-tar pitch	O
• Soot	O
• Sulfur mustard	O
• Diesel exhausts	E,O
Occupations	
• Aluminum production	O
• Coal gasification	O
• Coke production	O
• Hematite mining (underground)	O
• Iron and steel founding	O
• Painting	O
• Rubber production industry	O
Metals	
• Arsenic and inorganic arsenic compounds	E,O
• Beryllium and beryllium compounds	O

• Cadmium and cadmium compounds	O
• Chromium (VI) compounds	O
• Nickel compounds	O
Dust and fibers	
• Asbestos (all forms)	E,O
• Silica dust, crystalline	E,O
Personal habits	
• Coal, indoor emissions from household combustion	E
• Tobacco smoke, secondhand	E,O
Other exposures	
• Tobacco smoking	—
• MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)	—

Abbreviations: E, environmental exposure; IARC, International Agency for Research in Cancer; O, occupational exposure.

Symptoms and Signs

- Burning, lancinating pain
- Pain distribution typically has a neurological distribution, which can range from one nerve to many nerves to one nerve root to homuncular (i.e., that distribution included in a segment of affected brain tissue).
- Pain largely independent of activity. Often more noticeable at night, perhaps due to less distraction by other issues.
- Weakness. May be either neurological distribution similar to the pain distribution above. May also be more general to deconditioning, or avoidance of pain
- May have normal examination or may have abnormalities that include muscle weakness, sensibility decrements, stretch reflex abnormalities

Diagnosis

Initial Assessment

The initial assessment is focused on determining the type of neuropathic pain, which is most commonly categorized into three categories for which different treatment options are typically provided: central neuropathic pain, radicular neuropathic pain and peripheral neuropathic pain.

Diagnostic Criteria

Table 14. Diagnostic Criteria for Neuropathic Pain Categories

Probable Diagnosis of Neuropathic Pain	Symptoms, History	Signs	Tests
Central Neuropathic Pain	Burning, lancinating, independent of activity; weakness. History of, or symptoms of, transient ischemic attack, cerebrovascular accident, multiple sclerosis, cancer (especially lung, breast, colorectal, melanoma, renal)	May have normal examination or may have abnormalities that include muscle weakness, atrophy, sensibility decrements, stretch reflex abnormalities, gait disturbance. May have signs consistent with underlying diseases (see box to left for examples)	Magnetic Resonance Imaging of brain Lumbar puncture Fundoscopic (eye) exam. Tests for underlying diseases (e.g., chest x-ray, mammography, urinalysis, skin examination, colonoscopy, etc.)
Radicular Neuropathic Pain (See Low Back Disorders Guideline)	Burning, radiating pain in distribution of typically in only one nerve root. Sensory symptoms in the same dermatomal distribution(s) Myotomal symptoms in the same nerve root distribution as above sensory symptoms.	May have normal examination or may have abnormalities in usually only one myotomal/dermatomal distribution(s), including muscle weakness, atrophy, sensibility decrements, stretch reflex abnormalities.	Magnetic Resonance Imaging EMG/NCS
Peripheral Neuropathic Pain	Burning, lancinating, independent of activity; weakness May have symptoms of a systemic disease (e.g., diabetes mellitus, alcoholism, rheumatoid arthritis, lupus, HIV/AIDS)	May have normal examination or may have abnormalities that include muscle weakness, sensibility decrements, stretch reflex abnormalities, neurotrophic skin changes Signs of zoster, herpes simplex	EMG/NCS Glucose tolerance testing, fasting glucose and/or hemoglobin A1c if risks for diabetes mellitus Possible testing for alcohol (e.g., MCV, GGTP, hepatic enzymes) Rheumatological panels, ESR if concerns about those disorders

Classification

Neuropathic pain is generally classified into one of three categories:

- ***Central neuropathic pain*** is pain that develops due to central nervous system dysfunction (e.g., infarcts and brain tumors may cause pain). These are mostly not discussed in this guideline as these are almost always considered non-occupational disorders, unless the tumor is of occupational origin.
- ***Radicular neuropathic pain*** is pain in the extremities (arms, hands, legs, and/or feet) that is caused by an associated nerve being compromised ("pinched") in the spine. See Cervical and Thoracic Spine Disorders and Low Back Disorders Guidelines for management of those conditions.
- ***Peripheral neuropathic pain*** is most often due to non-occupational causes such as diabetes mellitus, alcohol abuse, vitamin deficiencies, infections, inherited traits, or as consequences of autoimmune disorders. While the principles of managing pain apply, medical management of those disorders are not included in this guidance, as they are beyond the scope of this Guideline.

Complex Regional Pain Syndrome is sometimes considered neuropathic pain. (Please see Guideline to manage this condition.)

Traumatic nerve injuries may occasionally cause peripheral neuropathic pain. Management of these traumatic nerve injuries is discussed in the appropriate ACOEM Guidelines.

Toxic occupational peripheral neuropathies are relatively uncommon and there are no quality studies of treatments. Interventions are primarily inferred based on treatment of two common, non-occupational peripheral neuropathies, diabetic neuropathy and postherpetic neuralgia. Peripheral neuropathies that are due to occupational exposures, such as n-hexane exposure, should be treated with elimination of the offending exposure – **Recommended, Insufficient Evidence (I)**. The pain from those occupational neuropathies that has persisted despite efforts to directly treat the underlying conditions should be managed in accordance with the principles of neuropathic pain treatment that are outlined in this Chronic Pain Guideline.

History

The history of neuropathic pain varies depending on the type of neuropathic pain. Regardless, the initial queries follow standard lines of questioning for patients with pain (e.g., function, onset, trauma history, location of pain, presence of tingling/numbness, aggravating factors, relieving factors). Initial queries should be sufficient to identify and categorize the neuropathic pain into one of the categories (central, radicular, peripheral). After preliminary categorization, additional questions should especially be asked to identify causal or contributing factors of each. Still, asking all questions across these categories is generally needed for the initial evaluation to assure proper categorization as well as identification of causal, aggravating, contributing factors.

Care should be taken to identify potential causal factors and address both occupational and non-occupational components to optimize the clinical outcome. A detailed occupational history to identify potentially causative factors is highly recommended. Some exposures may have industrial hygiene data available on request to help quantify exposures.

There are many causes of central neuropathic pain, thus a general approach is provided. The more common questions to particularly include regarding central neuropathic pain include any history of any type central nervous system dysfunction (e.g., transient ischemic attacks (TIAs), infarcts, lifetime history of cancer, brain tumors, spinal cord injury ([967-969], multiple sclerosis [949]. Infectious causes should be queried, including hepatitis C, HIV, syphilis, and herpest viruses. Autoimmune disease should be sought. Thoughtful queries to ascertain disorders not previously diagnosed are required (e.g., prior symptoms of TIAs that were ignored). Tumors most likely to metastasize to the brain include breast, lung, melanoma, colorectal and renal. Some lung cancers are particularly considered occupational due to significant occupational exposures (see work-relatedness section).

Questions to particularly include regarding radicular neuropathic pain include radiating pain in the extremities (arms, hands, legs, and/or feet). A history of spine disorders is often present. See Cervical and Thoracic Spine Disorders and Low Back Disorders Guidelines for evaluation and management of radicular neuropathic pain.

There are many causes of painful peripheral neuropathies.[999, 1000] This results in a highly heterogeneous clinical presentation that includes sensory, motor, and mixed sensory-motor neuropathies. A few examples of toxic neuropathies include acrylamide, arsenic, carbon disulfide, mercury, and n-hexane. The general approach is to particularly query regarding peripheral neuropathic pain include nerve trauma, post-surgical nerve injuries [963, 1068, 1069], entrapment neuropathies, diabetes mellitus, alcohol abuse, vitamin deficiencies (e.g., B6, B12), infections (zoster, herpes simplex, HIV, leprosy, syphilis) [1020, 1021], family history of neuropathy, rheumatoid arthritis, lupus and other autoimmune disorders. For those with history(ies) of these systemic disorders, questions addressing

duration and adequacy of control is important (e.g., history of lifetime maximum, typical and recent hemoglobin A1c measures; complications of rheumatoid arthritis).

Complex Regional Pain Syndrome is sometimes considered neuropathic pain. (Please see Guideline to manage this condition.)

Medical History Questionnaire

For radicular pain, please see either the Lumbar Spine Disorders Guideline and/or Cervical and Thoracic Spine Disorders Guideline.

For Complex Regional Pain Syndrome (CRPS), please see CRPS guidance within the Chronic Pain Guideline.

Physical Exam

Physical examination maneuvers should include a comprehensive neuromusculoskeletal exam to identify all positive and negative aspects in an attempt to secure a correct diagnosis. These maneuvers include observation, inspection, palpation, cranial nerve examination, range of motion, strength, stretch reflexes, coordination, balance, and sensory exam.

Signs of central neuropathic pain presentations are highly variable and depend on the diagnosis and precise neurological lesion(s). CVAs, MS and tumors all may present with heterogenous abnormal neurological symptoms and signs.

Signs of peripheral neuropathy differ based on the cause and distributions of lesions. Most are symmetrical and some are asymmetrical. The most common are due to diabetes and alcohol, thus most have symmetrical presentations (e.g., reduced monofilament sensation in both feet). Sensory neuropathies start with distal abnormalities in the lower extremities, usually including reduced sensation of fine touch that moves proximally as it becomes more severe. Later involvement of the fingers and hands is typical. Motor neuropathies more typically affect distal extremities prior to clinically affecting proximal extremities. Peripheral neuropathies due to trauma involve that distribution alone and are nearly always mixed sensory-motor, as most nerves have combined functions.

For radicular pain, please see either the Lumbar Spine Disorders Guideline and/or Cervical and Thoracic Spine Disorders Guideline.

For Complex Regional Pain Syndrome (CRPS), please see CRPS guidance within the Chronic Pain Guideline.

Diagnostic Recommendations

Laboratory Tests for Peripheral Neuropathic Pain

Recommended.

Laboratory tests are recommended as a screen to evaluate specific disorders (e.g., diabetes mellitus, alcohol) that may cause or contribute to peripheral neuropathic pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Indications:	Patients with peripheral neuropathies without prior diagnostic evaluations. Diagnostic testing should generally include fasting glucose and either hemoglobin A1c and/or 2-hour glucose tolerance testing. The threshold for testing for signs of alcohol should also be quite low (i.e., CBC with Mean Cell Volume, GGTP, AST and ALT). Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor.
Benefits:	Diagnosing a latent condition. As there is evidence that multiple disorders interact to raise risk of neuropathy, addressing all causes is also thought to produce a more favorable prognosis.
Harms:	Negligible
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated when either there is a significant change in exposure (e.g., substantial weight gain) or symptoms change.
Rationale:	Diagnosis or diabetes mellitus (or glucose intolerance) and alcohol abuse is important to treat to prevent peripheral neuropathy and progression [138-148]. Serological tests are minimally invasive, unlikely to have substantial adverse effects, are low to moderately costly depending on the specific test ordered, have evidence of diagnostic efficacy and are thus recommended for focused testing of a few diagnostic considerations.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: laboratory tests, blood glucose, thyroid function, thyroid function tests, cerebrospinal fluid; neuralgia, neuropathic pain; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 462 articles in PubMed, 10,643 in Scopus, 10 in CINAHL, 149 in Cochrane Library, 19,100 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.*

Measurement(s) of occupational neurotoxins is recommended to evaluate peripheral neuropathic pain. Examples include n-hexane [1025-1031, 1033, 1071], acrylamide [1034-1036], arsenic [1037-1046], carbon disulfide [1047-1057], lead [1058-1064], and mercury [1065, 1066].

Occupational Neurotoxin Exposure Measurement(s)

Recommended.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Indications:	Most workers with neuropathic pain who are exposed to n-hexane, acrylamide, arsenic, carbon disulfide, lead and/or mercury. There are other less common neurotoxins that may also require measurement, particularly based on the occupational and non-occupational histories and exposure(s). Rationale to not obtain measurements may include that the exposures were too long ago to be elevated from that exposure; still, measuring them may be relevant for non-occupational exposures and verifying the tests are negative. Previously obtained temporal measurements may potentially obviate the need to re-measure.
Benefits:	Assessing the probability of a work-related cause or material contribution. May provide evidence to reduce or eliminate exposure(s) and improve the prognosis.
Harms:	Negligible, however it is possible for both false positive and false negative testing results.
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated when there is a significant change in exposure (e.g., work processes change).
Rationale:	Occupational exposure measurements are not invasive, have no adverse effects, are moderate cost or high cost depending on the number of specific tests ordered, have evidence of accuracy when assayed in reputable labs, and are thus recommended for focused environmental testing to assist in the evaluation of patients with peripheral neuropathic pain.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: neurotoxin exposure, neurotoxins, acrylamide, thallium, lead, carbon disulfide; neuralgia, neuropathic pain, peripheral neuropathy; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 260 articles in PubMed, 1 in Scopus, 59 in CINAHL, 464 in Cochrane Library, 1,030 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL,*

0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

Antibodies to Confirm Specific Disorders

Strongly Recommended.

Antibodies are strongly recommended as a screen to confirm specific disorders (e.g., rheumatoid arthritis, lupus) and for assessing patients with chronic peripheral neuropathic pain

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Indications: Patients with peripheral neuropathies without prior diagnostic evaluations, or with incomplete evaluations. Diagnostic testing should generally include sedimentation rate. Other tests may include rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.

Benefits: Diagnosing an unknown condition. As there is evidence that multiple disorders interact to raise risk of neuropathy, addressing all causes is also thought to produce a more favorable prognosis.

Harms: Negligible

Frequency/Dose/Duration: One evaluation. A second evaluation may be indicated when either there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.

Rationale: Elevated antibody levels are highly useful for confirming clinical impressions of rheumatic diseases. However, routine use of these tests may result in inaccurate diagnoses due to false positives especially if there is a low pre-test probability. Measurement of antibody levels is minimally invasive, unlikely to have substantial adverse effects, and is low to moderately costly depending on the specific test ordered. They are recommended for focused testing of a few diagnostic considerations. However, ordering of a large, diverse array of antibody levels without diagnostically targeting a few specific disorders is not recommended.

Evidence: *A comprehensive literature search since 2012 was conducted using PubMed, EBSCO, and Cochrane Library using the following terms: antibodies, antibodies pain; chronic pain. We found and reviewed 9 articles in PubMed, 80 in EBSCO, 17 in Cochrane Library and 0 from other sources. We considered for inclusion 2 from PubMed, 1 from EBSCO, 0 from Cochrane Library and 0 from other sources. Of the 3 articles*

considered for inclusion, 1 randomized trials and 0 systematic studies met the inclusion criteria.

ANSAR Testing for Diagnosing Chronic Neuropathic Pain

Not Recommended.

ANSAR testing is not recommended to assist in diagnosing chronic neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: ANSAR has not been shown to alter the clinical management of patients with chronic neuropathic pain. The value of identifying abnormalities in autonomic tone, if they exist, has not been demonstrated. The value of pharmacologically treating such abnormalities if they are clinically silent and manifested by positive test results has also not been identified. ANSAR is non-invasive, has minimal risk of adverse effects depending on the maneuvers performed, but is moderately costly. ANSAR is not recommended for evaluation of patients with chronic neuropathic pain.

Evidence: *A comprehensive literature search since 2012 was conducted using PubMed, EBSCO, Cochrane Library and Google Scholar using the following terms: ANSAR, ANSAR testing, benzyl benzoate; chronic pain. We found and reviewed 0 articles in PubMed, 0 in EBSCO, 0 in Cochrane Library and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from EBSCO, 0 from Cochrane Library and 0 from other sources. Zero articles met the inclusion criteria.*

Non-specific Inflammatory Markers for Screening for Inflammatory Disorders

Recommended.

Erythrocyte sedimentation rate, CRP and other inflammatory markers are recommended for screening for signs of systemic inflammation among those with peripheral neuropathic pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications: Patients with peripheral neuropathies without prior diagnostic evaluations, or with incomplete evaluations. Subsequent, additional tests may be needed, including rheumatoid factor, antinuclear antibody level, and others. Testing is advisable even if other diagnostic testing finds another disorder (e.g., occupational neurotoxin) to assure there is not another, treatable, contributing factor, especially if explanation of the symptoms is incomplete.

Benefits:	Diagnosing an unknown condition. As there is evidence that multiple disorders interact to raise risk of neuropathy, addressing all causes is also thought to produce a more favorable prognosis.
Harms:	Negligible
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated when either there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.
Rationale:	Erythrocyte sedimentation rate is the most commonly used systemic marker for non-specific, systemic inflammation and is elevated in numerous inflammatory conditions as well as with infectious diseases. C-reactive protein has been linked with an increased risk of coronary artery disease. However, it is also a non-specific marker for other inflammation. Other non-specific markers of inflammation include ferritin, and an elevated protein-albumin gap, however those two markers appear to have no known clinical roles. CRP and ESR measurements are minimally invasive, have low risk of adverse effects and are low cost. They are recommended as a reasonable screen for systemic inflammatory conditions especially in patients with chronic neuropathic pain without clear definition of a diagnosis and/or with incomplete explanation of symptoms. However, test results should be interpreted cautiously as the specificity is not high. The ordering of a large, diverse array of anti-inflammatory markers without targeting a few specific disorders diagnostically is not recommended, as it the utility of such wide batteries of tests is dubious.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: non specific inflammatory markers, inflammation markers; neuralgia, neuropathic pain; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of tests, efficacy, and efficiency. We found and reviewed 39 articles in PubMed, 1,780 in Scopus, 0 in CINAHL, 20 in Cochrane Library, 21,000 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.*

Cytokine Tests for Diagnosing Chronic Neuropathic Pain

Not Recommended.

Routine testing with or the use of batteries of cytokine tests is not recommended to diagnose chronic neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:

Cytokines purportedly determine whether a patient is experiencing pain or has suffered a toxicological insult. However, there are no quality studies that address this premise. Available studies suggest that these markers may be elevated in chronic pain conditions, but these studies did not have adequate control groups and did not control for potential confounders. The range of disorders in which cytokines may be elevated also needs definition, as the current range of conditions appears large,[149-157] suggesting they are not specifically isolated to patients with chronic pain, and thus the specificity of these tests seems likely to be quite low.

A high-quality, 7-year study of 880 elderly subjects evaluated impacts of IL-6 and CRP on both cross-sectional associations with morbidity and long-term mortality.[149] CRP and IL-6 were higher among smokers at baseline and those with higher body mass indexes (BMIs). IL-6 and CRP were also higher among those with hypertension, myocardial infarction, stroke, elevated glycosylated hemoglobin levels, HDL, and number of chronic conditions. Both IL-6 and CRP were inversely related to quartiles of moderate and strenuous physical activity. CRP and/or IL-6 were associated with incidence of hypertension, myocardial infarction, diabetes, and incident cases of chronic conditions. Physical performance measures of changes in grip strength, signature time, chair-rise and 6-m fast walk all were not significant for IL-6 or CRP. Cytokines need to be rigorously studied to ascertain if there is a place for them in the evaluation and/or management of chronic pain conditions, including stratification for occupationally-relevant diseases. Documentation that the discovery of elevated cytokine levels results in changes in evaluation and/or clinical management would also be necessary. Alternatively, this testing may be useful if the absence of elevated cytokine levels would warrant concluding that a patient does not have a remediable physical cause of pain. While cytokine testing is minimally invasive, and has a low risk of adverse effects, these tests are high cost, with no evidence that they alter the clinical management of patients with chronic neuropathic pain. Their place in the evaluation of patients with chronic neuropathic pain is yet to be determined and cytokine testing is not recommended.

Evidence:

A comprehensive literature search since 2012 was conducted using PubMed, EBSCO, Cochrane Library, and Google Scholar using the following terms: cytokines; chronic pain; diagnostic tool, sensitivity, specificity, positive predictive value, and negative predictive value. We found and reviewed 3,871 articles in PubMed, 952 in EBSCO, 2 in Cochrane Library, 83,300 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 0 from EBSCO, 0 from Cochrane Library, 0 from Google Scholar, and 1 from other sources. Of the 2 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.

Needle EMG and Nerve Conduction Study to Diagnose

Recommended.

Needle EMG and Nerve Conduction Study is recommended for evaluation of select chronic neuropathic pain patients.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Indications:	Indications include the evaluation of symptoms that are either in one limb or are widespread. Includes the evaluation of potential radicular pain. Also includes the post-surgical population to evaluate the potential for a nerve conduction delay identifiable by NCS with inching/segmental technique. Generally not performed until there is failure to resolve after waiting 4 to 6 weeks to provide for sufficient time to develop EMG abnormalities (usually a minimum of 3 weeks to begin to show significant changes).
Benefits:	Diagnosing an unknown condition. Identification of a neurological conduction delay caused by a scar that is remediable.
Harms:	Negligible. Modest pain from the procedure
Frequency/Dose/Duration:	One evaluation. A second evaluation may be indicated when either there is a significant change in symptoms. It is also reasonable to repeat testing after a period of a year or two as initial testing is known to occasionally become positive with the passage of time.
Rationale:	EMG/NCS is often helpful for helping define the location and extent of neurological impairments. EMG/NCS is minimally invasive, has minimal adverse effects, is moderately costly, has been found to be diagnostically helpful and is thus recommended for diagnosis in select neuropathic pain patients.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: needle EMG, needle electromyography; neuralgia, neuropathic pain; diagnostic, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 41 articles in PubMed, 360 in Scopus, 0 in CINAHL, 0 in Cochrane Library, 5,710 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 0 randomized trials and 0 systematic studies met the inclusion criteria.*

Surface EMG for Diagnosing Chronic Neuropathic Pain

Not Recommended.

Surface EMG is not recommended for the differential diagnosis of chronic pain. There are selective indications for use with biofeedback.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: Surface EMG has no demonstrated value in the clinical evaluation or treatment of neuropathic pain with resultant altered management or improved clinical outcomes. Surface EMG may be of use in biofeedback training, and gait analysis for musculoskeletal and/or neurologic disorders, but it has no established use in the management of chronic neuropathic pain and is thus not recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: surface EMG, surface electromyography; neuralgia, neuropathic pain, chronic pain; diagnostic, diagnostic tool, diagnosis, sensitivity, specificity, positive predictive value, negative predictive value, predictive value of tests, efficacy, and efficiency. We found and reviewed 448 articles in PubMed, 4,507 in Scopus, 0 in CINAHL, 64 in Cochrane Library, 38,800 in Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.*

Functional MRIs for Diagnosing Chronic Neuropathic Pain

Not Recommended.

Functional MRIs are not recommended for diagnosing chronic neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Although there are research studies, there are no quality studies indicating that the findings on fMRIs are of sufficient sensitivity and specificity to permit identification of the presence or absence of chronic neuropathic pain or to distinguish between different types of chronic pain states. The clinical applications of the test have not been defined. Functional MRI is minimally invasive and has low adverse effects, is high cost, but has no quality evidence of efficacy and is thus not recommended.

Evidence: *A comprehensive literature search since 2012 was conducted using PubMed, EBSCO, Cochrane Library, and Google Scholar using the following terms: functional MRI; chronic pain; diagnostic tool,*

sensitivity, specificity, positive predictive value, and negative predictive value. We found and reviewed 13,450 articles in PubMed, 200 in EBSCO, 8 in Cochrane Library, 84,500 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from EBSCO, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

Local Anesthetic Injections for Diagnosing Chronic Neuropathic Pain

Recommended.

Local anesthetic injections are recommended for diagnosing chronic neuropathic pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications:	Chronic neuropathic pain in a specific nerve distribution (e.g., ilioinguinal, genitofemoral) that is otherwise unexplained by other investigation, including imaging, EMG/NCS.
Benefits:	Potential to identify a potentially treatable lesion
Harms:	Medicalization, nerve trauma, and continuing a search for a fixable lesion if one is not to be found.
Frequency/Dose/Duration:	Once.
Rationale:	Local injections (e.g., ilioinguinal, genitofemoral nerve blocks) have not been evaluated in sizable, quality studies for diagnostic, prognostic, or treatment purposes, though they may assist with diagnosis and consideration of potential treatment options and are thus recommended. However, corticosteroid or neuroablative injections/procedures for localized pain for these nerve blocks are not recommended as the risk of increased pain, local tissue reaction, and neuroma outweigh documented benefits (see Table 15).
Evidence:	*A comprehensive literature search since 2012 was conducted using PubMed, EBSCO, Cochrane Library, and Google Scholar using the following terms: local anesthetic injections; chronic pain; diagnostic tool, sensitivity, specificity, positive predictive value, and negative predictive value. We found and reviewed 522 articles in PubMed, 84 in EBSCO, 3 in Cochrane Library, 40,000 in Google Scholar, and 0 from other sources. We considered for inclusion 3 from PubMed, 0 from EBSCO, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Of the 3 articles considered for inclusion, 0 randomized controls trials and 1 systematic review met the inclusion criteria.*

Table 15. Adverse Effects of Injections

General complications of neuraxial injections, and of injections near the paravertebral muscles	Infection at site and remote (meningitis found in one German study following trigger point, facet, and epidural injections). Bleeding, including hematoma causing nerve compromise. Direct trauma to nerve, causing permanent damage or increased pain. Injection into the wrong space (artery, vein, inadvertent intrathecal, or thoracic cavity). This can lead to respiratory compromise, cardiac arrest, or pneumothorax.
Complications specifically related to the substance and amount injected (in addition to possible anaphylaxis)	Local anesthetics – seizures, cardiac collapse. Sympatholytics – hypotension, tachycardia, cardiac dysrhythmias. Corticosteroids* – endocrine dysfunction, diabetes, hypertension, dysphoria, immune compromise, phlebitis, muscle pain, osteoporosis, dependency, rarely nerve damage, etc. Baclofen* – anxiety, blurred vision, ataxia, coma, depression, dizziness, dysarthria, dystonic reaction, hallucinations, headache, respiratory depression, seizures, stroke, etc. Botulinum toxins – weakness, paralysis, respiratory compromise, diplopia, dizziness, injection site reaction.

*These adverse effects are mostly temporary aggravations and dependent on dose and frequency.

SPECT/PET for Diagnosing Chronic Neuropathic Pain

Not Recommended.

SPECT is not recommended to evaluate patients with chronic neuropathic pain (aside from use in cases of suspected inflammatory arthropathies not diagnosed by more common tests). The use of PET scanning is also not recommended to evaluate patients with chronic neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: SPECT and PET scanning of the brain may be of use in assessing the status of cerebrovascular perfusion, tumors, and neurodegenerative conditions, but aside from providing information of interest for research, these techniques have not been shown to be useful in influencing the management of patients with chronic neuropathic pain. SPECT scanning may be useful in detecting inflammatory disease in the spine and other areas that might not be amenable to evaluation by other studies. SPECT and PET scanning are minimally invasive, have negligible adverse effects, are high cost, have no quality evidence of efficacy for diagnosis of neuropathic pain, and so are not recommended.

Evidence: *A comprehensive literature search since 2012 was conducted using PubMed, EBSCO, Cochrane Library, and Google Scholar using the following terms: single proton emission computer tomography, SPECT, positron emission tomography; chronic pain; diagnostic tool, sensitivity, specificity, positive predictive value, and negative predictive value. We found and reviewed 1607 articles in PubMed, 319 in EBSCO, 17 in Cochrane Library, 32,300 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from EBSCO, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero*

articles met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed, EBSCO, Cochrane Library, and Google Scholar using the following terms: positron emission tomography, PET; chronic pain; diagnostic tool, sensitivity, specificity, positive predictive value, and negative predictive value. We found and reviewed 3,563 articles in PubMed, 1,142 in EBSCO, 10 in Cochrane Library, 50,500 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from EBSCO, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

FCEs for Chronic Neuropathic Pain

Recommended.

FCEs are recommended for evaluating patients with chronic neuropathic pain to attempt to objectify worker capability vis-à-vis either specific job or general job requirements.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications:	Need to objectify worker capabilities compared with either job specific or general job requirements. Should generally be performed only after treatment options have been utilized, implemented, and stability has been reached with apparent residual deficits,
Benefits:	Assess functional abilities and may facilitate greater confidence in return to work.
Harms:	Medicalization, worsening of pain with testing. May have misleading results that understate capabilities.
Frequency/Dose/Duration:	Generally only once unless there is significant passage of time or apparent change in function.
Rationale:	FCEs are one of the few means to attempt to objectify limitations and are frequently used in the workers' compensation system. Because their reliability and validity have not been proven and there are issues with suboptimal efforts that are not necessarily captured, they should be considered as one set of data about what a patient was willing to do on a given day. They should not be used to override the judgment about the work ability of a patient. They particularly should not be viewed as providing objective evidence when there is other corroborating evidence of subjective-objective mismatches or evidence the patient is able to accomplish more than was demonstrated at the time of the FCE. Most patients will not require an FCE, particularly where the patient is able to articulate a desire to return to work, along with stated capabilities that appear to match the clinical impression. An FCE may be

helpful in identifying capabilities at an end of healing for purposes of attempting to support work limitations that are used to assign "permanent" restrictions and disability applications. However, providers should be particularly aware of major secondary gain issues when FCEs are performed for these purposes and be particularly vigilant about test-retest reliability, test validity measures, and the need to unequivocally report all measures as well as any evidence of subjective-objective mismatches.

Evidence:

A comprehensive literature search since 2012 was conducted using PubMed, EBSCO, Cochrane Library, and Google Scholar using the following terms: functional capacity evaluations, FCEs; chronic pain; diagnostic tool, sensitivity, specificity, positive predictive value, and negative predictive value. We found and reviewed 186 articles in PubMed, 35 in EBSCO, 10 in Cochrane Library, 49,900 in Google Scholar, and 0 from other sources. We considered for inclusion 0 from PubMed, 0 from EBSCO, 0 from Cochrane Library, 0 from Google Scholar, and 0 from other sources. Zero articles met the inclusion criteria.

Treatment Recommendations

Activity Modification and Exercise

Bed Rest for Neuropathic Pain

Not Recommended.

Bed rest is not recommended for neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Rationale:

There is no evidence that bed rest is helpful for these conditions and it has been found to be unhelpful for LBP and other conditions. There are potential adverse effects that reportedly have included venous thromboses and pulmonary emboli (see Low Back Disorders guideline). Bed rest, although not invasive, has potential for major adverse effects, is costly, has no documented benefits, and thus it is not recommended.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized*

controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of bed rest for the treatment of neuropathic pain or diabetic neuropathy.*

Aerobic Exercise for Neuropathic Pain

Recommended.

Aerobic exercise is selectively recommended for treatment of neuropathic pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications: Moderate to severe neuropathic pain; diabetes mellitus and/or significant de-conditioning. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's *Guidelines for Exercise Testing and Prescription,* 9th ed.,[161] in regards to health screening and risk stratification.

Benefits: Improved function, improved endurance, improved neuropathy control if diabetes is contributing

Harms: Negligible. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Intolerance of weight bearing in severe lower extremity osteoarthrosis. Other musculoskeletal disorders possible (e.g., plantar heel pain).

Frequency/Dose/Duration: Start with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Transition to home exercise program. The most detailed program for low back pain was walking at least 4 times a week at 60% of predicted maximum heart rate (220-age = maximum heart rate) is recommended.[162] Benchmarks were 20 minutes during Week 1, 30 minutes during Week 2, and 45 minutes after that point. Nearly all patients should be encouraged to maintain aerobic exercises on a long-term basis additionally to maintain optimal health.

Indications for Discontinuation: Non-tolerance, failure to progress, development of another disorder, or reaching a 4 to 6 week timeframe.

Rationale: There is one moderate quality trial with a combination of aerobic, strengthening and stretching compared with an education control that suggested a trend towards efficacy [1072]. Aerobic exercise is not invasive, has negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, has strong rationale for select indications, and thus is selectively recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of aerobic exercise for the treatment of neuropathic pain or diabetic neuropathy. There is low-quality evidence listed in Appendix 4.*

Strengthening Exercise for Neuropathic Pain

Recommended.

Strengthening exercise is selectively recommended for treatment of neuropathic pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications: Moderate to severe neuropathic pain; diabetes mellitus and/or significant strength deficits. However, those with significant cardiac disease or significant potential for cardiovascular disease should be evaluated prior to instituting vigorous exercises, following the American College of Sports Medicine's *Guidelines for Exercise Testing and*

	Prescription, 9th ed.,[161] in regards to health screening and risk stratification.
Benefits:	Improved function, improved strength, improved ability to perform strength-demanding job tasks
Harms:	Negligible. Theoretical risk of myocardial infarction and angina in a severely deconditioned patient. Other musculoskeletal disorders possible (e.g., plantar heel pain).
Frequency/Dose/Duration:	Typically start with 3 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Supervised treatment frequency and duration is dependent on symptom severity and acuity and the presence of comorbid conditions. Transition to including home exercises.
Indications for Discontinuation:	Non-tolerance, failure to progress, development of another disorder (e.g., strain), or reaching a 4 to 6 week timeframe.
Rationale:	There is one moderate quality trial with a combination of aerobic, strengthening and stretching compared with an education control that suggested a trend towards efficacy [1072]. Patients who have significant deconditioning with strength deficits, particularly with mismatches between abilities and job demands are strong candidates for strengthening exercises. Strengthening exercises are not invasive, have negligible adverse effects, may be low cost when self-administered to moderate cost in aggregate, have strong rationale for select indications, and thus are selectively recommended.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Aquatic Therapy for Neuropathic Pain

Recommended.

A trial of aquatic therapy is selectively recommended for patients with neuropathic pain, who meet the referral criteria for supervised exercise therapy and have co-morbidities (e.g., extreme obesity, significant degenerative joint disease, etc.) that preclude effective participation in a weight-bearing physical activity.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications:	Moderate to severe neuropathic pain; non-weight bearing status or partial weight-bearing; diabetes mellitus and/or significant de-conditioning
Benefits:	Improved function, improved endurance, improved neuropathy control if diabetes is contributing
Harms:	Negligible
Frequency/Dose/Duration:	Start with 3 to 4 visits a week; demonstrate evidence of functional improvement within first 2 weeks to justify additional visits. Program should include up to 4 weeks of aquatic therapy with progression to a land-based, self-directed physical activity or self-directed aquatic therapy program by 6 weeks. For some patients with chronic neuropathic pain, aquatic exercise may be the preferred method. In these few cases, the program should become self-managed and if any membership to a pool is covered, coverage should be continued if it can be documented that the patient is using the facility at least 3 times a week and following the prescribed exercise program.
Indications for Discontinuation:	Non-tolerance, failure to progress, or reaching a 4 to 6 week timeframe.
Rationale:	There is no quality evidence that aquatic exercise is helpful for treatment of neuropathic pain. However, there are circumstances where aquatic exercise may be indicated for treatment of patients with neuropathic pain. These include patients who are either non-weight-bearing or limited weight-bearing and have diabetes mellitus that is co-contributing to their neuropathic pain and others who have significant deconditioning due to neuropathic pain. Aquatic exercise is not invasive, has negligible adverse effects, is moderate cost in aggregate, has rationale for select indications, and thus is selectively recommended.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized,*

randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of aquatic therapy for the treatment of neuropathic pain or diabetic neuropathy.*

Physical or Occupational Therapy for Neuropathic Pain

No Recommendation.

There is no recommendation for or against the use of physical or occupational therapy to treat neuropathic pain. (See individual treatments that are often administered by these professionals.)

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Studies are heterogeneous with numerous simultaneous interventions, thus sound conclusions cannot be drawn from them.[168-185] See individual treatment modalities to ascertain the available evidence on specific treatment interventions, including exercises and other treatments.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled*

clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of physical or occupational therapy for the treatment of neuropathic pain or diabetic neuropathy.*

Medications

NSAIDs have been used in the treatment of neuropathic pain conditions [1073].

NSAIDs for Chronic Neuropathic Pain

Recommended.

NSAIDs are recommended for treatment of chronic neuropathic pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications: Neuropathic pain sufficiently severe to require medication. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as second-line medications, often after tricyclic or SNRI anti-depressants are utilized which have considerably greater evidence of efficacy. In some patients, NSAIDs may be the preferred initial therapy due to the low adverse effect profile in working age adults. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious. Over-the-counter (OTC) agents may suffice and may be tried first. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended as second-line medications. Third-line medications should include one of the other generic medications. COX-2 selective agents are recommended as a fourth- or fifth-line medications when there are contraindications for other NSAIDs and/or there are risks of GI complications; however, concomitant treatment with misoprostol, sucralfate, and proton pump inhibitors are also options for gastro-protection.

Benefits: Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. NSAIDs are among the best medications especially for safety sensitive workers.

Harms: Gastrointestinal adverse effects are especially prominent in those with a past history of gastrointestinal bleeding, for which either cytoprotection or Cox-2 agents are advisable. Those elderly, with

diabetes mellitus and rheumatological orders also are among those at increased risk. There is some evidence for increased cardiovascular risks, especially in the highly and more-selective NSAID agents. There is no clear evidence of cardiovascular harm from the non-selective NSAIDs ibuprofen and naproxen. (see further discussion in Low Back Disorders). It appears that despite widespread usage, diclofenac does not have clear superiority at least for LBP where it has been trialed, yet may have increased risks for adverse cardiovascular events[188] and is neither recommended nor not recommended for use either alone or in combination with misoprostol (Arthrotec).

Frequency/Dose/Duration: For most patients, scheduled dosage, rather than as needed, is preferred to avoid adverse effects of other treatment options, but prescribing NSAIDs as needed is reasonable for mild or moderate symptoms. Due to the potential adverse effects from chronic use (more than 2 months) of NSAIDs, patients should be periodically monitored for adverse effects such as hypertension, blood loss, renal insufficiency (as manifested by an increased creatinine), and hepatic enzyme elevations. Older patients and those with co-morbidities may require more frequent monitoring. Use of an adjunctive cytoprotective agent may also be warranted.

Indications for Discontinuation: Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale: There is one moderate quality trial with trend towards efficacy of a Cox-2 inhibitor [1074]. There is another moderate quality trial of topical diclofenac for treatment of neuropathic pain [1075]. NSAIDs are not invasive, have low adverse effects in employed populations, are low cost, have evidence of efficacy for radicular pain and thus inferred for other neuropathic pain and are thus recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for*

inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Acetaminophen for Neuropathic Pain

Recommended.

Acetaminophen is recommended for treatment of chronic neuropathic pain, particularly in patients with contraindications for NSAIDs.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications:	Neuropathic pain sufficiently severe to require medication. Generally, generic ibuprofen, naproxen or other older generation NSAIDs are recommended before acetaminophen. Acetaminophen is a reasonable alternative, or can be used as an adjunct, although evidence suggests it is modestly less efficacious.
Benefits:	Improved pain control with negligible risks of impairments, especially cognitive, which are present with many other treatment options. Acetaminophen is among the best medications especially for safety sensitive workers.
Harms:	Negligible if used as prescribed. Renal adverse effects are possible, especially among chronic, high-dose users and those with other renal impairment. Hepatic toxicity in high doses or among those with other hepatic impairments (e.g., excessive alcohol consumption). Reduced dosage may be used in such settings, along with close monitoring.
Frequency/Dose/Duration:	Generally prescribed up to 3.5g/day in divided doses, usually QID dosing.
Indications for Discontinuation:	Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.
Rationale:	There are no quality trials of acetaminophen for treatment of neuropathic pain. This drug does have evidence of efficacy for treatment of LBP, although not as successful as diflunisal,[189] mefenamic acid,[190] indomethacin,[190] or aspirin.[190] Thus, while the evidence suggests efficacy of acetaminophen (also called paracetamol), it appears these medications are modestly less efficacious than NSAIDs (although generally safer) at least for LBP. Acetaminophen is not invasive, has very low adverse effects, is low cost, has evidence of efficacy for treatment of LBP and is thought to have modest efficacy and thus is recommended for treatment of neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of acetaminophen for the treatment of neuropathic pain or diabetic neuropathy.*

Tricyclic antidepressants (e.g., amitriptyline, desipramine, nortriptyline) have been used for the treatment of neuropathic pain [1073, 1076-1089] SNRIs have also been used for the treatment of neuropathic pain [1090-1096][1097].

Tricyclic, Tetracyclic and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) Anti-depressants for Neuropathic Pain

Recommended.

Tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRIs) are moderately recommended for treatment of neuropathic pain.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Indications: Neuropathic pain sufficiently severe to require medication. Anti-depressants are considered among the first-line agents to treat neuropathic pain. Several of the anti-depressants may also be used to take advantage of the sedating properties for nocturnal sleep disturbance due the neuropathic pain. One trial suggested superiority of combination therapy of nortriptyline with gabapentin compared to each drug alone (O'Connor 09), while another suggested superiority of combining amitriptyline 25mg/day with pregabalin 75mg BID [1098].

Benefits: Improved pain control, may include reduced sleep disturbance.

Harms: Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Dry mouth, constipation, suicide risk, urinary retention, glaucoma, QT prolongation, sinus tachycardia, dizziness, weight gain. Cardiotoxicity.

Frequency/Dose/Duration: Prescribe at a low dose at night and gradually increase (e.g., amitriptyline 25mg QHS, increase by 25mg each week) until a sub-maximal or maximal dose is achieved, sufficient effects are achieved, or adverse effects occur. Duration of use for chronic neuropathic pain patients may be indefinite, although some patients do not require indefinite treatment, particularly if they are compliant with the elements of a functional restoration program. One reportedly efficacious combination was nortriptyline 100 mg with gabapentin 3600 mg per day (O'Connor 09), while another was amitriptyline 25mg/day with pregabalin 75mg BID [1098].

Indications for Discontinuation: Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale: There are multiple moderate quality trials of tricyclic/tetracyclic and SNRI antidepressants that included desipramine, amitriptyline, nortriptyline, clomipramine, duloxetine, venlafaxine. [1099, 1100][1098, 1101-1104]; [1095, 1096][1097]. All quality data suggest efficacy. Comparable efficacy was been shown between amitriptyline and duloxetine, as well as between amitriptyline and nortriptyline [1105]. One trial suggested combination therapy of nortriptyline with gabapentin was superior to single drug arms and another trial suggested superiority of a combination of amitriptyline and pregabalin [1098]. One study involving maprotiline did not show efficacy when compared to amitriptyline [1102]. Tricyclic antidepressants are not invasive, have adverse effects that range from modest to intolerable, are low cost, have evidence of efficacy for treatment of neuropathic pain and are recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective,*

and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Selective serotonin reuptake inhibitors have been used to treat neuropathic pain.

SSRIs, Selective Serotonin Reuptake Inhibitors (Escitalopram, Mirtazapine, Fluoxetine, or Trazodone) and Norepinephrine-Dopamine Reuptake Inhibitors (NDRI) (e.g., Bupropion) for Neuropathic Pain

Recommended.

SSRI antidepressants and NDRI antidepressants are selectively recommended for the treatment of Neuropathic Pain.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

Indications: Neuropathic pain sufficiently severe to require medication. Tricyclic, tetracyclic and SNRI anti-depressants are considered among the first-line agents to treat neuropathic pain. SSRI antidepressants have substantially less evidence of efficacy and thus should generally be considered 2nd or 3rd line agents.

Benefits: Modestly improved pain control.

Harms: QT prolongation, increased suicide risk, dry mouth, trouble sleeping. Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Serotonin syndrome.

Frequency/Dose/Duration: Regimens used in the quality trials include escitalopram 20mg/day [1106, 1107], bupropion SR 150mg/day [1108], and up to 60mg/day of fluoxetine. Duration of use for chronic neuropathic pain patients may be indefinite, although some patients do not require indefinite treatment, particularly if they are compliant with the elements of a functional restoration program.

Indications for Discontinuation: Resolution of pain, sufficient improvement to not require medication, lack of efficacy, development of adverse effects.

Rationale: There are 5 moderate quality studies evaluating selective serotonin reuptake inhibitors for neuropathic pain. Data suggest modest efficacy. As SSRI antidepressants have evidence of efficacy for treatment of fibromyalgia, but have little evidence of efficacy for treatment of chronic pain conditions (see Low Back Disorders Guideline), the mechanism of potential efficacy for neuropathic pain is unclear. As one

trial suggested potentially superior results with desipramine, and evidence is more robust for the other anti-depressants, treatment with tricyclics and SNRIs as initial prescriptions is generally recommended before SSRIs. Selective serotonin reuptake inhibitors, bupropion, escitalopram, mirtazapine, fluoxetine and trazodone are not invasive, have moderate adverse effects, are low to moderate cost, have limited evidence of efficacy and are thus selectively recommended for treatment of neuropathic pain. SSRIs may separately be indicated for the treatment of depression, although an agent that also has greater evidence of efficacy against chronic neuropathic pain may be a better option.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is moderate-quality evidence incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Antipsychotics for Neuropathic Pain

No Recommendation.

There is no recommendation for or against the use of antipsychotics for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies of anti-psychotics for the treatment of neuropathic pain.

Antipsychotics are not invasive, have adverse effects, are low to moderate cost and in the absence of evidence of efficacy, there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of antipsychotics for the treatment of neuropathic pain or diabetic neuropathy. There is low quality evidence-listed in Appendix 4.*

Anti-convulsant agents have been used in the treatment of neuropathic pain [1077, 1089, 1109, 1110]. Gabapentin and Pregabalin have been used for the treatment of postherpetic neuralgia. [1078-1080, 1111, 1112][1083, 1084, 1113-1128][1129, 1130]. Pregabalin has been used in the treatment of neuropathic pain [1077, 1092, 1093, 1131, 1132]. Pregabalin has been used for the treatment of diabetic peripheral neuropathy and its complications [200-202, 780, 1133-1136][728, 1137-1143]. Mirogabalin is closely related to both gabapentin and pregabalin but with higher potency [1144, 1145].

Valproate (VPA), and its valproic acid, sodium valproate, and divalproex sodium, are medications primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches and they are not typically used for neuropathic pain.

Anti-convulsant Agents (Gabapentin, Pregabalin, Mirogabalin, Gabapentin Enacarbil, Lamotrigine, Topiramate, Carbamazepine and Oxcarbazepine) for Neuropathic Pain

Recommended.

Anti-convulsants are moderately recommended for treatment of neuropathic pain.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **High**

Indications:	Moderate to severe painful neuropathic pain sufficient neuropathic pain to require medication. Generally, anti-convulsants are considered a potential adjunct as a second- or third-line treatment for chronic neuropathic pain, after attempting other treatments (e.g., anti-depressants, aerobic exercise, other exercise).
Benefits:	Modest pain reduction. May include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs. Also may have adverse effects including nausea, vomiting, dizziness, confusion, somnolence and weight gain.Carbamazepine may be associated with fluid and electrolyte abnormalities. Topiramate may cause kidney stones and ocular toxicity.
Frequency/Dose/Duration:	Frequency and dosing are based on the medication prescribed. Duration of use for neuropathic pain patients may be indefinite, although many of these patients do not require indefinite treatment as the condition usually often resolves or improves. Gabapentin dose is initiated usually at 300mg/day and gradually raised.
Indications for Discontinuation:	Resolution of pain, lack of efficacy, intolerance, or development of adverse effects. Monitoring of employed patients is indicated due to elevated risks for CNS-sedating adverse effects.
Rationale:	There is high and moderate quality evidence of efficacy for multiple anti-convulsants (Gabapentin, Pregabalin, Lamotrigine, Carbazepime and Topiramate) for treatment of peripheral neuropathic pain in comparison with placebo [199][200, 201][191-194, 198, 202]. Although not all studies are positive [195, 196, 1146, 1147], the highest quality studies and those with larger sample sizes suggest efficacy. Nearly all quality evidence is of peripheral neuropathic pain, although at least one quality trial included MS patients [192]. There is not evidence that adding lamotrigine to gabapentin is efficacious [192]. Comparable efficacy has been suggested when comparing gabapentin and nortriptyline [1120]. In a study by Otto 2004, Valproic acid did not prove efficacious, however, in another study divalproex showed efficacy for post-herpetic neuralgia when compared to placebo at 8 weeks [1148]. Anti-convulsants are not invasive, have some adverse

effects, are moderate cost, have some quality evidence of efficacy for treatment of neuropathic pain and are recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is high-quality and moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Oral acyclovir has been used for the prevention of postherpetic neuralgia [1149-1151].

Anti-virals (Acyclovir, Valacyclovir, Famciclovir) for Neuropathic Pain

No Recommendation.

There is no recommendation for the use of antivirals to treat neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Two moderate quality placebo-controlled trials conflict regarding efficacy of acyclovir and included 9-year followup data. One trial found comparable results between valacyclovir and famciclovir, but had not placebo control [1151]. In a study with oral acyclovir the incidence of post-herpetic neuralgia was not reduced [1152] and in Acosta 2001, only 10% of study participants reported pain reduction. In a study by Huff 1988, 1993, median pain duration was 20 days in acyclovir treated individuals vs 62 days in placebo but the study also noted that the absence of pain at the onset of cutaneous herpes zoster did not preclude later development of the disease. A study using amantadine was inconclusive [1153]. It has been suggested that the medication

needs to be administered within 2 days to be effective. Anti-viral medications are not usually invasive, have low adverse effects, are moderate cost, but in the absence of evidence of efficacy, there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Homeopathy and Complementary Medicines for Neuropathic Pain

No Recommendation.

There is no recommendation for or against the use of Harpagoside, willow bark (Salix), Camphora molmol, Melaleuca alternifolia, Angelica sinensis, Aloe vera, Thymus officinalis, Menthe piperita, Arnica montana, Curcuma longa, Tanacetum parthenium, St. John's wort, nutmeg, Neuragen PN, Vitamin E and Zingiber officinale[285] for chronic neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:

One moderate quality trial of topical sprays of nutmeg added to methyl salicylate, menthol and coconut oil found lack of efficacy [1154]. Another trial found lack of efficacy for St. John's Wort [1155]. An experimental study of Neuragen suggested ultra-short term efficacy [1156], but there were no clinical trial results of short or long term results. Homeopathic and complementary medications are not invasive, have generally low adverse effects, are low to moderate cost but in the absence of quality evidence of efficacy, there is no

recommendation. They also may have interactions with other prescribed medications.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is moderate-quality evidence incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Clonidine has been used in the treatment of peripheral neuropathy [1157].

Clonidine for Neuropathic Pain

No Recommendation.

There is no recommendation for or against use of clonidine for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies of clonidine for treatment of neuropathic

Pain, although there are some studies of parenteral use. Clonidine is not invasive, has adverse effects, is low to moderate cost cumulatively and in the absence of evidence of efficacy, there is no recommendation.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective,*

and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of clonidine for the treatment of neuropathic pain or diabetic neuropathy.*

Dextromethorphan, an NMDA agent, has been used in the treatment of neuropathic pain [1158].

Dextromethorphan for Neuropathic Pain

Recommended.

Dextromethorphan is selectively recommended for treatment of select patients with neuropathic pain.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

Indications:	Patients with diabetic neuropathy or other peripheral neuropathies who have failed NSAIDs, TCAs, and anti-convulsant agents, including gabapentin and pregabalin.[1159]
Benefits:	Improved pain control, may include reduced sleep disturbance.
Harms:	Sedating properties may be intolerable. For some, the sedation is sufficient to impair daytime activities and thus, especially in those cases, be inappropriate for safety sensitive jobs.
Frequency/Dose/Duration:	Doses range widely. In the successful trial, an average daily dose of 400mg was utilized. Dextromethorphan is recommended in doses that are on average at least 3 times higher than the antitussive dose, and carefully titrated to therapeutic effect. Duration for patients with chronic neuropathic pain generally be limited to 2 or 3 months as there is no evidence of long-term safety, although longer periods of use may be reasonable.
Indications for Discontinuation:	Resolution of neuropathic pain, lack of efficacy, development of adverse effects.

Rationale:

There are no quality studies evaluating NMDA receptor/antagonists other than dextromethorphan.[207-209] However, the multiple quality studies of dextromethorphan involve many different patient populations and, in aggregate, somewhat conflict on whether there is meaningful benefit. One trial suggested differences based on diagnoses, with diabetic neuropathy patients, but not postherpetic neuralgia patients responding.[1160] A trial of largely central neuropathic pain was negative.[1161] The balance of evidence suggests that dextromethorphan may have modest morphine-sparing effects in limited circumstances, while memantine appears inferior to dextromethorphan. There is evidence that dextromethorphan reduces pain in diabetic neuropathy patients. One study found that dextromethorphan plus morphine for treatment of malignant pain resulted in a reduction in the number of episodes of pain breakthrough requiring additional medication,[1162] but another study in which dextromethorphan was combined with NSAIDs, dextropropoxyphene, or morphine found no significant analgesic effects.[1163] An experimental model of pain in healthy subjects also has reportedly failed to confirm dextromethorphan's additional benefits beyond morphine.[1164] There is insufficient evidence to support the use of amantadine and memantine and of low doses of dextromethorphan. The two published studies of high doses of dextromethorphan show relief in painful diabetic neuropathy, but not in postherpetic neuralgia. The basic concept of NMDA antagonism in neuropathic pain appears sound, but these agents also have high adverse effects. Thus, there is a need for quality studies and perhaps development of newer agents with fewer CNS adverse effects. Dextromethorphan is not invasive, has high adverse effects, has limited evidence of efficacy in some patient populations with neuropathic pain and thus is selectively recommended after failure of multiple other medications.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met*

the inclusion criteria. There are high-quality and moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Muscle Relaxants for Acute Exacerbations of Neuropathic Pain

Recommended.

Muscle relaxants are selectively recommended for brief use as a second- or third-line agent in acute exacerbations of neuropathic pain with muscle spasms.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications:	Moderate to severe neuropathic pain with musculoskeletal manifestations, especially muscle spasm. (See Low Back Disorders Guideline for other detailed indications). Not indicated for ongoing chronic pain treatment.
Benefits:	Improvement in muscle spasm and pain related to muscle spasm
Harms:	Sedation, intolerance, medicalization
Frequency/Dose/Duration:	Due to abuse potential, carisoprodol is not recommended. Chlorzoxazone and chlormezanone are also not indicated due to incidence of adverse effects. Otherwise initial dose in evening (not during workdays or if patient operates a motor vehicle, though daytime use acceptable if minimal CNS-sedating effects). If significant daytime somnolence results, particularly if it interferes with performance of conditioning exercises and other components of the rehabilitation process or treatment plan, discontinue or prescribe a reduced dose. Duration for exacerbations of chronic pain is limited to a couple weeks. Longer term treatment is generally not indicated.
Indications for Discontinuation:	Resolution of pain, non-tolerance, significant sedating effects that carry over into the daytime, other adverse effects.
Rationale:	There are no quality studies evaluating muscle relaxants for treatment of neuropathic pain. However, they have been evaluated in quality studies evaluating chronic back and neck pain,[211-213] although there are far more studies on acute LBP (see Low Back Disorders guideline).[214] The quality of the studies comparing these agents to placebo are likely overstated due to the unblinding that would be inherent in taking a drug with substantial CNS-sedating effects. The adverse effect profile is concerning.[215] Most concerning is the significant potential for CNS sedation, which has typically ranged between 25 to 50%. There are some studies indicating more than 50% of the patients are affected by CNS sedation. Thus, prescriptions for skeletal muscle relaxants for daytime use should be carefully weighed against the patient's need to drive vehicles, operate machinery, or

otherwise engage in occupations where mistakes in judgment may have serious consequences. Skeletal muscle relaxants also have a modest, but significant potential for abuse[216] and their use in those with a history of any substance abuse or dependence should be with caution. They are low cost if generic medications are prescribed. Skeletal muscle relaxants are not recommended for continuous management of subacute or chronic spine pain or other chronic musculoskeletal disorders, although they may be reasonable options for select acute pain exacerbations or for a limited trial as a third- or fourth-line agent in more severely affected patients in whom NSAIDs and exercise have failed to control symptoms.

Diazepam appears to be inferior to other skeletal muscle relaxants,[212, 217] has a higher incidence rate of adverse effects, and is addictive. **Therefore, diazepam is not recommended for use as a skeletal muscle relaxant.** Evidence suggests that carisoprodol is comparable to cyclobenzaprine. Chlorzoxazone has been associated with hepatocellular toxicity. Chlormezanone has been implicated in Stevens-Johnson syndrome and toxic epidermal necrolysis. Carisoprodol is particularly prone to abuse and thus, carisoprodol, chlorzoxazone and chlormezanone are **not recommended.**

Muscle relaxants are not invasive, have significant adverse effects, are low to moderately costly and do not have evidence of efficacy to treat neuropathic pain. However, they have indications for short term treatment of muscle spasms and exacerbations and are selectively recommended.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of muscle relaxants for the treatment of neuropathic pain or diabetic neuropathy.*

Magnesium For Neuropathic Pain

Not Recommended.

Magnesium is not recommended for the treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: There are two moderate quality studies of magnesium for treatment of neuropathic pain with both suggesting lack of efficacy. [1165, 1166]. Magnesium is non-invasive orally or minimally invasive if IV, has low to moderate adverse effects, is low to moderate cost, but with evidence of inefficacy is not recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.*

Tumor Necrosis Factor-alpha Blockers for Neuropathic Pain

No Recommendation.

There is no recommendation regarding TNF-alpha blockers for treatment of chronic neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: TNF-alpha blockers have not been evaluated in quality studies.[223, 224] TNF-alpha blockers are minimally invasive, have adverse effects, are high cost and in the absence of efficacy there is no recommendation.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of TNF-alpha blockers for the treatment of neuropathic pain or diabetic neuropathy.*

Topical NSAIDs for Chronic Pain Where Target Tissue Superficially Located

Recommended.

Topical NSAIDs are selectively recommended for treatment of neuropathic pain.

Strength of Evidence – **Recommended, Evidence (C)**

Level of Confidence – **Low**

Indications: Neuropathic pain that includes superficial pain generation (e.g., postherpetic neuralgia) [1075], peripheral nerve injury, and possibly some toxic neuropathies with superficial pain generation.

Benefits: Improved pain control

Harms: Dry skin, erythema, pruritus, irritation, paresthesias. Allergies to adhesives in patches may occur.

Frequency/Dose/Duration: Diclofenac 1.5% lotion TID was used in the one quality trial. [1167]

Indications for Discontinuation: Adverse effects, intolerance, sufficient improvement to no longer require treatment.

Rationale: There is one moderate quality trial showing efficacy of diclofenac lotion 1.5% for treatment of neuropathic pain from post-herpetic neuralgia and CRPS [1167]. Another moderate quality trial suggested efficacy of topical aspirin. Yet one moderate quality trial suggested aspirin superiority but not for diclofenac or indomethacin. However, the target tissue for neuropathic pain is often too deep for clear justification of use of topical NSAIDs. Topical NSAIDs are not invasive, have low adverse effects, are high cost for a typical treatment regimen, have evidence of efficacy for post-herpetic neuralgia and so are recommended for neuropathic pain with superficial pain generation.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.*

Different topical creams have been used to treat neuropathic pain [1168, 1169]

Other Topical Creams (Ketamine, Amitriptyline and Combination Ketamine and Amitriptyline)

Not Recommended.

Strength of Evidence **Moderately Not Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Rationale: There are 2 moderate quality studies trialing other topical creams, both suggesting lack of efficacy. On study used 5% ketamine cream for diabetic neuropathy patients [1169] and another used 2% amitriptyline,

1% ketamine or a combination of 1% ketamine and 2% amitriptyline combined on patients with post-herpetic neuralgia [1168]. These creams are non-invasive, have relatively moderate cost but due to the lack of efficacy are not recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Capsaicin has been used with different preparation for the treatment of neuropathic pain [1170-1174]

Capsaicin Patches for Neuropathic Pain

Moderately Recommended.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Indications: Neuropathic pain that includes superficial pain generation (e.g., postherpetic neuralgia), peripheral nerve injury, and possibly some toxic neuropathies with superficial pain generation. Most data suggest lack of efficacy for diabetic neuropathy and painful polyneuropathy [1175, 1176]

Benefits: Improved pain control

Harms: Erythema, burning, pain, pruritus, irritation

Frequency/Dose/Duration: One capsaicin patch applied for 60 minutes, with improvements lasting up to 12 weeks [1177-1180]. One open label extension suggested the

benefits may last to 12 months [1181]. One trial also suggested efficacy of capsaicin cream 0.075% TID to QID for 6 weeks for post-herpetic neuralgia [1182].

Indications for Discontinuation: Adverse effects, intolerance, sufficient improvement to no longer require treatment.

Rationale: Multiple moderate quality trials suggest efficacy of capsaicin patches for treatment of post-herpetic neuralgia [1177, 1179, 1180, 1183-1185]. However, two trials of capsaicin cream for treatment of neuropathic pain were negative [1175, 1176]. One capsaicin patch is not invasive, has low adverse effects, is high cost, has evidence of efficacy for treatment of superficial neuropathic pain and thus is recommended.

One trial of capsaicin gel and another for capsaicin cream for diabetic neuropathy and painful polyneuropathy respectively suggest a lack of efficacy. [1175, 1176]

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Lidocaine, especially in the form of patches, has been used in the treatment of postherpetic neuralgia and neuropathic pain [1077, 1087, 1186, 1187, 1188, 1189].

Lidocaine Patches for Neuropathic Pain

Moderately Recommended.

Lidocaine patches are moderately recommended for treatment of postherpetic neuralgia when there is localized pain amenable to topical treatment.

Strength of Evidence – **Moderately Recommended, Evidence (B)**

Level of Confidence – **Moderate**

Indications:	Moderate to severe peripheral neuropathic pain that includes superficial pain generation (e.g., postherpetic neuralgia), peripheral nerve injury, and possibly some toxic neuropathies with superficial pain generation [1190-1192]. One quality trial [1193] evaluated treatment of CTS with pain as a central complaint when other treatable causes of the pain have been eliminated and after more efficacious treatment strategies, such as splinting and glucocorticosteroid injection(s), have been attempted.
Benefits:	Modest improvements in pain
Harms:	Dermal irritation and intolerance; may have adverse systemic effects if widespread applications of numerous patches
Frequency/Dose/Duration:	Lidocaine patch 5%, up to 4 patches applied up to 12 hrs/day. Duration of use may be ongoing for chronic, localized pain, although most patients do not require indefinite treatment. Caution is warranted regarding widespread use of topical anesthetics for potential systemic effects from widespread administration.[221] Topical 5% lidocaine medicated plaster has also been used [1194-1197], as well as lidocaine spray [1198]
Indications for Discontinuation:	Resolution, intolerance, adverse effects, lack of benefits, or failure to progress over a trial of at least 2 weeks.
Rationale:	Lidocaine patches have been reportedly effective for treatment of localize peripheral neuropathic pain [1190-1192]. Topical lidocaine has been suggested to improve pain associated with CTS and appears to be somewhat more effective than naproxen.[222] This provides some basis for a consensus recommendation for treatment of peripheral neuropathic pain. Lidocaine patches are not invasive, generally have a low adverse effect profile, are moderately costly, have some evidence of efficacy for treatment of carpal tunnel syndrome and thus are recommended for treatment of peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one high-quality study and moderate-quality studies incorporated into this analysis.*

Physical Methods and Devices

Motor cortex stimulation has been used in the treatment of chronic neuropathic pain [1200-1202].

Motor Cortex Stimulation for Neuropathic Pain

Not Recommended.

Motor cortex stimulation is not recommended for the treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale:

A moderate quality trial suggested lack of efficacy of motor cortex stimulation for neuropathic pain [1203]. However, for spinal cord injury, cranial electrotherapy was suggested to be effective in another trial [1204] and another low-quality trial with implanted electrodes for thalamic syndrome suggested some efficacy [1205]. Motor cortex stimulation is not invasive, has low adverse effects, is moderate cost, has evidence of lacking efficacy and thus is not recommended.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized,*

randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.*

Magnets and Magnetic Stimulation for Neuropathic Pain

Not Recommended.

Magnets and magnetic stimulation are not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **High**

Rationale: There is no significant evidence base from which to draw conclusions on the utility of magnets as a treatment modality for neuropathic pain, although quality studies of other musculoskeletal disorders have not shown any indication for use of magnets for treatment. Magnets are not invasive, have no adverse effects, are low cost, have no quality evidence of efficacy and are thus not recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized*

controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are two moderate-quality studies incorporated into this analysis.*

Taping and Kinesiotaping for Neuropathic Pain

Not Recommended.

Taping and kinesiotaping are not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: Taping and kinesiotaping have not been shown effective in quality studies for the treatment of chronic neuropathic pain. Taping and kinesiotaping are not invasive, have some adverse effects, are moderate cost to high cost depending on length of treatment, have no evidence of efficacy and thus are not recommended for neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies that evaluate the usage of taping or kinesoitaping for the treatment of neuropathic pain or diabetic neuropathy.*

Self-application or Healthcare Provider Application of Cryotherapies for Neuropathic Pain

No Recommendation.

There is no recommendation for or against the self-application of cryotherapies for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Self-application of cryotherapies have not been shown effective in quality studies for the treatment of chronic neuropathic pain. Cryotherapies are not invasive, have minimal adverse effects, are moderate cost depending on length of treatment, have no evidence of efficacy and thus there is no recommendation.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the self-application of cryotherapies for the treatment of neuropathic pain or diabetic neuropathy.*

Diathermy for Neuropathic Pain

Not Recommended.

There is no recommendation for or against diathermy for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Diathermy has not been shown effective in quality studies for the treatment of chronic neuropathic pain. Diathermy is not invasive, has minimal adverse effects, is moderate cost depending on length of treatment, has no evidence of efficacy and thus there is no recommendation regarding peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one-moderate quality study incorporated into this analysis.*

Ultrasound

Sometimes Recommended.

There is no recommendation for or against the use of ultrasound for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies of ultrasound for the treatment of neuropathic pain. Ultrasound is not invasive, has few adverse effects, but is moderately costly. In the absence of quality evidence, there is no recommendation for or against ultrasound for treating neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized*

controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of ultrasound for the treatment of neuropathic pain or diabetic neuropathy.*

Provider-Based or Self-Application of Infrared Therapy for Neuropathic Pain

Not Recommended.

Infrared therapy is not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: Infrared therapy was reportedly ineffective in one moderate quality study for the treatment of chronic diabetic neuropathic pain [1206]. Infrared therapy is not invasive, has minimal adverse effects, is moderate cost depending on length of treatment, has no evidence of efficacy and thus is not recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled*

clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are two moderate-quality studies incorporated into this analysis.*

Low-level Laser Therapy for Neuropathic Pain

Not Recommended.

Low-level laser therapy is not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: Low level laser therapy has not been shown effective in quality studies for the treatment of chronic neuropathic pain. Low level laser therapy is not invasive, has minimal adverse effects, is high cost depending on length of treatment, has no evidence of efficacy and thus there is no recommendation for peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.*

Manipulation for Neuropathic Pain

No Recommendation.

There is no recommendation for treatment of neuropathic pain. There may be other indications for manipulation (e.g., see Low Back Disorders Guideline including for radicular pain).

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is no quality evidence of efficacy of manipulation for treatment of neuropathic pain. Spine indications are addressed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines. Manipulation is not invasive, has some adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy and thus there is no recommendation for or against manipulation for treatment of peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of manipulation for the treatment of neuropathic pain or diabetic neuropathy.*

Massage for Neuropathic Pain

No Recommendation.

There is no recommendation for or against the use of massage for patients with neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is no quality evidence of efficacy of massage for

treatment of neuropathic pain. Spine indications are addressed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines. Massage is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy and thus there is no recommendation for or against massage for treatment of neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of massage for the treatment of neuropathic pain or diabetic neuropathy.*

Mechanical Massage Devices for Neuropathic Pain

Not Recommended.

The use of mechanical massage devices applied by rehabilitation service providers or massage therapists to administer massage is not recommended for neuropathic pain.[238-240]

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is no quality evidence of efficacy of massage devices for treatment of neuropathic pain. Spine indications are addressed in the Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines. There is evidence reviewed that suggests devices are less effective than traditional massage. Massage devices are not invasive, have minimal adverse effects, are moderately costly, have no quality evidence of efficacy, and thus are not recommended for treatment of neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of mechanical massage devices for the treatment of neuropathic pain or diabetic neuropathy.*

Myofascial Release for Neuropathic Pain

No Recommendation.

There is no recommendation for myofascial release for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is no quality evidence of efficacy of myofascial release for treatment of neuropathic pain. Myofascial release is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy and thus there is no recommendation for or against myofascial release for treatment of peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of myofascial release for the treatment of neuropathic pain or diabetic neuropathy.*

Acupuncture and electroacupuncture have been used for the treatment of postherpetic neuralgia, occipital neuralgia and acute zoster [1207] [1208]. Peripheral nerve adjustment has been used for neuropathic pain [1209].

Acupuncture/Electroacupuncture

Not Recommended.

Acupuncture or electroacupuncture are not recommended to treat neuropathic pain.

Strength of Evidence – **Not Recommended, Evidence (C)**

Level of Confidence – **Low**

Rationale: None of three moderate quality trials evaluating acupuncture of electroacupuncture for treatment of neuropathic pain show efficacy [1210-1212], although one of the 3 studies showed a trend towards efficacy [1212]. Acupuncture is minimally invasive, has minimal adverse effects, is moderately costly, and in the absence of quality evidence of efficacy, is not recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Reflexology for Neuropathic Pain

Not Recommended.

Reflexology is not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: There are no quality studies of reflexology for treatment of neuropathic pain. Reflexology has not been shown beneficial for the treatment of chronic neuropathic pain. It also has not been shown to be beneficial for treatment of LBP in a moderate-quality study.[266] Reflexology is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy for any condition, and thus reflexology is not recommended for treatment of neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of reflexology for the treatment of neuropathic pain or diabetic neuropathy.*

High-voltage Galvanic Therapy for Neuropathic Pain

No Recommendation.

There is no recommendation for high-voltage galvanic therapy for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies of high-voltage galvanic therapy for treatment of neuropathic pain. High-voltage galvanic therapy is not proven efficacious for the treatment of chronic LBP or other chronic pain conditions. The single quality study suggests possible minimal, brief improvement for neck pain.[267] High-voltage galvanic therapy is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, and thus there is no recommendation for or against high-voltage galvanic therapy for treatment of neuropathic pain. It is not recommended for central neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of high-voltage galvanic therapy for the treatment of neuropathic pain or diabetic neuropathy.*

H-Wave® Device Stimulation for Neuropathic Pain

No Recommendation.

There is no recommendation for or against H-Wave® Device Stimulation for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies of H-Wave® Device Stimulation for treatment of neuropathic pain. H-Wave® Device Stimulation is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus there is no recommendation for or against H-Wave® Device Stimulation for treatment of neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of H-Wave® Device Stimulation for the treatment of neuropathic pain or diabetic neuropathy.*

Interferential Therapy for Neuropathic Pain

No Recommendation.

There is no recommendation for or against interferential therapy for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies of interferential for treatment of neuropathic pain. Interferential is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus there is no recommendation for or against interferential for treatment of peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of interferential therapy for the treatment of neuropathic pain or diabetic neuropathy.*

Iontophoresis for Neuropathic Pain

No Recommendation.

There is no recommendation for or against iontophoresis for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:

One moderate quality study of iontophoresis with vincristine suggested a lack of efficacy [1213]. There are no quality studies of iontophoresis with other medications for treatment of neuropathic pain. Iontophoresis is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus there is no recommendation for or against iontophoresis for treatment of peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.*

Microcurrent Electrical Stimulation for Neuropathic Pain

Not Recommended.

Microcurrent electrical simulation is not recommended for treatment of neuropathic pain.

Strength of Evidence – Not Recommended, Evidence (C)

Level of Confidence – **Low**

Rationale: One moderate quality trial suggested lack of efficacy of microcurrent transcutaneous electric nerve stimulation for treatment of neuropathic pain. Microcurrent is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of efficacy, thus is not recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.*

PENS for Neuropathic Pain.

No Recommendation.

There is no recommendation for or against PENS for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: One moderate quality experimental trial of PENS included only one treatment and suggested some efficacy, but included no intermediate to long term outcomes and suggested it required additional trials to ascertain clinical efficacy [1214]. PENS is minimally invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality evidence of clinical efficacy, thus there is no recommendation for or against PENS for treatment of peripheral neuropathic pain. It is not recommended for central neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.*

TENS for Neuropathic Pain

No Recommendation.

There is no recommendation for or against TENS for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no high-quality sham-controlled trials of TENS for treatment of neuropathic pain. There are mostly unblinded studies with suggestions of modest efficacy (Kumar 98 [1215-1217]. TENS is not invasive, has minimal adverse effects, is moderate to high cost in aggregate, has no quality sham-controlled evidence of efficacy, thus there is no recommendation for or against TENS for treatment of peripheral neuropathic pain. TENS may be a reasonable alternative for

those who fail all other non-invasive interventions and continue to have symptoms sufficiently severe to require other treatment.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one high-quality study and moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Repetitive transcranial magnetic stimulation (rTMS) has been used in the treatment of neuropathic pain [1201, 1202, 1218-1221].

Repetitive Transcranial Magnetic Stimulation (rTMS) for Neuropathic Pain

No Recommendation.

There is no recommendation for or against repetitive transcranial magnetic stimulation.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are several moderate and low quality studies using rTMS for the treatment of neuropathic pain [1201, 1202, 1218-1221] with no evidence of long-term efficacy and only some short term modest efficacy. R TMS is moderately invasive, has some adverse effects, is moderate cost, but due to lack of significant long-term efficacy, there is no recommendation.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled*

clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.*

Sympathetic Electrotherapy

Not Recommended.

Sympathetic electrotherapy is not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality studies of sympathetic electrotherapy for treatment of neuropathic pain. Sympathetic electrotherapy is not invasive, likely has relatively minor adverse effects, but is costly and in the absence of quality evidence of efficacy is not recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized*

controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of sympathetic electrotherapy for the treatment of neuropathic pain or diabetic neuropathy.*

External Radiation for Sympathetic Blockade for Neuropathic Pain

Not Recommended.

External radiation for sympathetic blockade is not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: While external radiation has been used to treat CRPS, available quality studies suggest it is not effective.[230] There is no quality evidence of efficacy for external radiation for treatment of neuropathic pain. External radiation is not invasive, has adverse effects, moderate to high cost, has no quality evidence of efficacy and thus, is not recommended for treatment of neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.*

Injection Therapies

Corticosteroids have been used to treat as well as to prevent zoster-associated pain in post-herpetic neuralgia [1089, 1222-1224][1225].

Corticosteroids for Neuropathic Pain

No Recommendation.

There is no recommendation for the use of corticosteroids for neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: One moderate quality trial suggested a combination of methylprednisolone plus midazolam was superior to either agent alone for treatment of post-herpetic neuralgia [1226], yet as the steroid group was the least effective of the three arms, it raises questions about the utility of glucocorticoids for treatment of neuropathic pain. Another study showed only a slight trend favoring a single epidural injection of methylprednisolone plus bupivacaine over standard care [1224]. Epidural injections are invasive, have adverse effects, are high cost and in the absence of clear evidence of efficacy, there is no recommendation.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is moderate-quality evidence incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Immunoglobulin has been used to treat neuropathic pain. [1227, 1228]

Immunoglobulin for Neuropathic Pain

No Recommendation.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: One moderate quality, unblinded trial suggested improved polyneuropathy pain with immunoglobulin at 4 weeks compared with standard care [1227]. A second moderate quality trial suggested improved post herpetic neuralgia pain at 4 weeks [1228]. Immunoglobulin is invasive, has some adverse effects, is high cost and in the absence of clear evidence of enduring efficacy, there is no recommendation.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of immunoglobulin for the treatment of neuropathic pain or diabetic neuropathy.*

Ketamine Infusion for Neuropathic Pain

Not Recommended.

There is no recommendation for or against ketamine infusion for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:

There are no quality studies of ketamine infusion for intermediate to long term. There are high-quality experimental studies suggest that intravenous ketamine can lead to pain reductions in patients with chronic neuropathic pain, this reduction paralleled the length of the infusion with follow-up periods of 160 minutes or less. Adverse effects were considerable. [278, 279] Lower, oral doses have been associated with lightheadedness, dizziness, tiredness, headache, bad dreams, and sensory changes. Ketamine has high abuse potential and when used as a general anesthetic leads to direct myocardial depression in addition to respiratory depression. Ketamine is invasive, has adverse effects (e.g., respiratory depression and hallucinations), is moderately costly, has very short term evidence suggesting efficacy but has not been shown to be efficacious over intermediate to longer durations and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are two high-quality studies incorporated into this analysis.*

Intrapleural Bupivacaine Infusions for Neuropathic Pain

Not Recommended.

Intrapleural bupivacaine infusions are not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: Intrapleural bupivacaine infusions have not been evaluated in sizable quality studies for diagnostic, prognostic, or treatment purposes regarding neuropathic pain. These infusions are invasive, have potential adverse effects, are costly, have no evidence of efficacy and thus are not recommended for treatment of neuropathic pain patients.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of intrapleural bupivacaine infusions for the treatment of neuropathic pain or diabetic neuropathy.*

Lidocaine Infusion for Neuropathic Pain

No Recommendation.

There is no recommendation for or against the use of lidocaine infusions for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:

There are many high- or moderate-quality studies evaluating the short-term safety and effectiveness of this treatment. Disorders studied principally included diabetic neuropathy,[273-276] CRPS,[277] spinal cord injury,[278] and post-operative pain.[279] The longest duration of follow-up with reported data appears to be 14 days,[275, 276] with most studies reporting results for less than 1 day. Most study results have been positive,[274-277] but some have been negative.[278, 279] Overall response rates among neuropathic pain patients reported are approximately 10 to 50%.[276, 278, 279] No intermediate or long-term quality studies on treatment efficacy have been reported. There is one pilot study that suggests a duration of improvement of 4 hours[277] and a few suggesting improvements for up to 14 days.[276, 277] There are no quality studies that show relief up to or beyond 1 month. The available data suggest duration of pain relief is proportionate to the dose administered.[276, 277] One cohort of 99 neuropathic pain patients reported 42% of patients had at least a 30% reduction in pain.[280] The same author recommended restriction of this procedure to those patients who could not take oral medications.[281] There is no evidence that these infusions result in a sustained decrease in pain medication requirements, reported pain, or an increase in overall function. Lidocaine infusions are invasive, have significant, dose-related adverse effects,[276, 277, 279] and are moderate to high cost depending on the number of treatments. While an adverse event would not be expected to be common, it could be serious or catastrophic. Thus, the intensity of monitoring required is unclear. Duration of treatment success is neither demonstrated nor predicted to be intermediate to long term. Repeated infusions without objective evidence of prolonged efficacy and functional improvement are not recommended. There are no large, quality studies evaluating the safety and effectiveness of this treatment. Lidocaine infusions are invasive, have adverse effects, are high cost, have not been evaluated in sizable, quality studies for diagnostic, prognostic, or treatment purposes and thus there is no recommendation.

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in*

PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one high-quality study and one moderate-quality study incorporated into this analysis.

Intravenous Phenytoin for Neuropathic Pain

No Recommendation.

There is no recommendation for or against the use of Phenytoin infusions for treatment of neuropathic pain

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies that evaluate the usage of intravenous phenytoin for the treatment of neuropathic pain or diabetic neuropathy.*

Adenosine has been used for treatment of neuropathic pain [1230-1233].

Intravenous Adenosine for Neuropathic Pain

Not Recommended.

Intravenous adenosine is not recommended for the treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: There are few quality trials of systemic adenosine infusion for treatment of neuropathic pain. There are no short term or long term benefits from adenosine infusion for neuropathic pain ([1231], although in the Eisenach study, intrathecal not intravenous adenosine was superior for reducing tactile allodynia. These treatments are invasive, have potential adverse effects, are costly, have no quality evidence of intermediate to longer-term efficacy and thus are not recommended for treatment of neuropathic pain patients.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Monoclonal Antibody Injections for Neuropathic Pain

No Recommendation.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are few quality trials of monoclonal antibody infusions for treatment of neuropathic pain. One high quality study using Tanezumab showed some modest efficacy for neuropathic pain reduction at the highest doses [1234]. In another study, Fulranumab was trialed but due to clinical concerns, the study was terminated [1235]. Additionally, there are no long-term benefits yet identified from monoclonal antibody infusion for neuropathic pain ([1231], although in the Eisenach study, intrathecal not intravenous adenosine was superior for reducing tactile allodynia. These treatments are invasive, have adverse effects, are costly, have no quality evidence of intermediate to longer-term efficacy and thus there is no recommendation for treatment with monoclonal antibodies in for neuropathic pain patients.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one high-quality study and moderate-quality studies incorporated into this analysis.*

Dorsal ganglion destruction has been attempted for treatment of neuropathic pain.

Dorsal Ganglion Destruction for Neuropathic Pain

Not Recommended.

Dorsal ganglion destruction is not recommended for treatment of neuropathic pain.

Strength of Evidence – **Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Rationale: There are no quality trials of dorsal ganglion destruction for treatment of neuropathic pain. These treatments are invasive, have potential adverse effects, are costly, have no quality evidence of efficacy and thus are not recommended for treatment of neuropathic pain patients.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are no quality studies evaluating the usage of dorsal ganglion destruction for the treatment of neuropathic pain or diabetic neuropathy. There is low-quality evidence listed in Appendix 4.*

Nerve blocks have been used in the treatment of selected neuropathic pain conditions [1236, 1237]. Various injections have also been used to attempt to both prevent [1238, 1239] and treat zoster [1226, 1240-1242].

Nerve Blocks for Neuropathic Pain

Recommended.

Nerve blocks are selectively recommended for treatment of neuropathic pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications:	Peripheral nerve entrapment with pain consistent with that one or two entrapped peripheral nerves, unresponsive to other treatments. One moderate quality trial of intercostal neuralgia [1236] and another at the site of the nerve injury [1237].
Benefits:	Improvement in chronic pain
Harms:	Infection, bleeding, allergic reaction, lack of improvement
Frequency/Dose/Duration:	One trial used depo-methylprednisolone 80 mg plus lidocaine 0.5% [1237]. Another used weekly injections of betamethasone 1mL (dose unspecified) plus 5mL ropivacaine 0.75% plus vitamin B12 1mg [1236]. Repeated injections should only occur if, and until there is incremental functional gain that continues to improve until reaching a plateau.
Indications for Discontinuation:	N/A
Rationale:	One trial used depo-methylprednisolone 80 mg plus lidocaine 0.5% and found benefits persisting to 3 months [1237]. Steroid plus anesthetic injection nerve blocks are invasive, have adverse effects, are moderate to high cost, have limited evidence that suggests some potential efficacy, and thus are selectively recommended.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Botulinum Toxin A injections have been used in the treatment of selected neuropathic pain conditions. [1243-1245].

Botulinum Toxin A (BTX_A) for Neuropathic Pain

Recommended.

Botulin Toxin A (BTX-A) injections are selectively recommended for neuropathic pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Indications:	For debilitating pain associated with post-herpetic neuralgia not responsive to first and second line therapies [1244, 1246] or for peripheral neuropathic pain [1243]. May be reasonable treatment for other focal neuropathy that is resistant to other treatment, such as decompression if indicated. Treatment not recommended for systemic neuropathic pain.
Benefits:	Improvement in chronic pain
Harms:	Infection, bleeding, allergic reaction, lack of improvement
Frequency/Dose/Duration:	Single injection of 100 IU of BTX-A (5U/ route) diluted with 4 mL of 0.9% sodium chloride injected Subcutaneously in a chessboard manner in all affected sites with a 1 cm space between injection sites. [1243, 1244]
Rationale:	One trial used BTX-A for sustained pain reduction for up to 12 weeks post injection when compared to placebo [1243]. Another study reported sustained effects for up to 14 weeks [1244]. In another trial, 5 u/ml BTX-A was compared to both 0.5% lidocaine and placebo. All 3 groups showed improvement at day 7 and 3 months post injection with a significantly better result in the BTX-A group. [1245]. BTX-A injections are invasive, have adverse effects, are moderate to high cost, have limited evidence that suggests some potential efficacy, and thus are selectively recommended.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using*

PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.*

Surgical Considerations

Surgical decompression has been used in the treatment of selected neuropathic pain conditions.

Surgical Decompression for Neuropathic Pain

Recommended.

Surgical decompression is selectively recommended for treatment of neuropathic pain.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**

Level of Confidence – **Moderate**

Indications: Pain consistent with peripheral nerve entrapment. Often this is consistent with a prior injury and scarring. Nerve conduction study is often helpful to confirm conduction delay at the same location as prior trauma. Prognosis is thought to be superior if the surgery is performed within 6 months of injury.

Benefits: Resolution of chronic pain

Harms: Surgical risks without significant improvement

Rationale: There are no quality trials of surgical decompression of entrapped peripheral nerves. However, there are case series with evidence of efficacy. Surgical decompression is invasive, has adverse effects, is high cost, but has a long history of efficacy in carefully selected cases, and thus is selectively recommended.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other*

sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.*

Spinal cord stimulation has been used in the treatment of selected neuropathic pain conditions [1114, 1247-1251].

Spinal Cord Stimulation for Neuropathic Pain

No Recommendation.

There is no recommendation for the use of spinal cord stimulation in the treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There are no quality sham-controlled trials for treatment of neuropathic pain, precluding an assessment of efficacy of SCS for treatment of neuropathic pain. There is one low quality trial with a standard care bias suggesting potential benefit at up to 6 months (Duarte 16). There are trials amongst patients with spine and leg pain (see Low Back Disorders guideline) and others for CRPS (see above). One trial comparing usual care, suggested superiority of SCS [1250]. One small, low quality experimental trial suggested preference for high-frequency to low-frequency stimulation [1248] and another experimental study evaluated sub-perception thresholds [1249]. SCS is invasive, has adverse effects, is high cost, but in the absence of significant evidence of efficacy, there is no recommendation for or against treatment of neuropathic pain.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other*

sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There is one moderate-quality study incorporated into this analysis. There is low-quality evidence listed in Appendix 4.*

Intrathecal Drug Delivery Systems for Chronic Nonmalignant Pain Conditions

Not Recommended.

Intrathecal drug delivery systems are not recommended for treatment of neuropathic pain.

Strength of Evidence **– Not Recommended, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale:

Intrathecal drug delivery systems using opioids have not been evaluated in quality studies for treatment of neuropathic pain. Intrathecal drug delivery systems may be potentially beneficial in limited situations (e.g., those involving malignant pain conditions and terminal patients) but these situations are beyond the scope of this guideline.) Intrathecal opioid delivery systems are invasive, have significant adverse effects including fatalities, potential long-term sequelae from both implantation/retention of the devices, including granuloma formation, and those associated with the concurrent use of intrathecal opioids.[284] These systems could potentially be indicated in those who have failed multiple trials of different oral medications and other treatments and have undergone independent psychological consultation including psychometric testing that does not reveal a contraindication to implantation. Patients considered for implanted opioid delivery systems should be evaluated regarding their suitability for protracted use of systemic opioids. They should have documented compliance with all chronic oral opioids treatment criteria, previously shown to be responsive to oral opioids with documented improved function (but unmanageable adverse effects that use of these systems would be able to overcome).

Evidence:

A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, and Google Scholar without date limits using the following terms: neuropathic pain, nerve pain, neuralgia; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective,*

and prospective studies. We found and reviewed 1413 articles in PubMed, 917 in Scopus, 176 in CINAHL, 9,630 in Google Scholar and 0 from other sources. We considered for inclusion 349 from PubMed, 0 from Scopus, 12 from CINAHL, 0 from Google Scholar and 0 from other sources. Of the 361 articles considered for inclusion, 238 randomized controlled trials and 123 systematic reviews met the inclusion criteria. A comprehensive literature search since 2012 was conducted using PubMed using the following terms: diabetic neuropathy; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 2423 articles in PubMed and 0 from other sources. We considered for inclusion 19 from PubMed and 0 from other sources. Of the 19 articles considered for inclusion, 13 randomized controlled trials and 0 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis.*

Ziconotide for Chronic Nonmalignant Pain Conditions

No Recommendation.

There is no recommendation for or against ntrathecal drug delivery systems with ziconotide for treatment of neuropathic pain. See Opioids guideline for use with opioids.

Strength of Evidence – **No Recommendation, Insufficient Evidence (I)**

Level of Confidence – **Low**

Rationale: There is one trial of only 6 days for treatment of chronic non-malignant pain with intrathecal administration after failure of opioids (Wallace 06) that suggested short term benefits. However, there are no trials of sufficient duration to provide evidence-based recommendations for treatment in chronic pain patients.

Evidence: A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Neuropathic Pain, Neuralgia; Ziconotide; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 6 articles in PubMed, 8 in Scopus, 0 in CINAHL, 1450 in Google Scholar, and 1 from other sources. We considered for inclusion 0 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Google Scholar, and 1 from other sources. Of the 1 article considered for inclusion, 1 randomized controlled trial and 0 systemic studies met the inclusion criteria. There is one moderate-quality study incorporated into this analysis.

Evidence Tables

Cytokines

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Taaffe 2000 (score = 8.0)	Cytokines	Prospective Cohort Study	No mention of sponsorship or COI.	N = 880 age 70-79 participants with chronic inflammation from MacArthur Study of Successful Aging	Mean age is 74/3 years/ 412 males, 468 females.	Plasma IL-6, CRP levels determined by enzyme-linked immunosorbent assay and log transformed to normalize distributions. Physical function measures: handgrip strength, signature time, chair stands, 6-m walk time.	Follow up at baseline of 7 years.	Women had lower (p <0.05) IL-6 levels. Hours per year undertaking moderate and strenuous physical activity also related to inflammatory markers with higher (p <0.001) IL-6 and CRP levels in less active individuals.	"Although IL-6 has been shown to predict onset of disability in older persons and both IL-6 and CRP are associated with mortality risk, these markers of inflammation have limited associations with physical performance, except for walking measures and grip strength at baseline, and do not predict change in performance 7 years later in a high-functioning subset of older adults."	According to the authors, baseline IL-6 and CRP not associated with change in performance.

Exercise

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Toth, 2014 (score= 4.5)	Exercise	RCT	No COI and sponsored by an unrestricted grant from the Department of Clinical Neurosciences, Faculty of Medicine, and University of Calgary, Calgary, AB, Canada.	N = 54 patients with NeP associated with a peripheral neuropathic process as well as chronic pain.	Mean age 55.1 years; 22 males,32 females	Exercise intervention group (N=28): 2 hours each month for 6 months with recommended 3-5 weekly workouts vs Education Intervention group (N=26): received 2 hour session once a month for 6 months	6 months	Exercise group reduced VAS pain severity by 7.9±2.8 mm compared to education group with 3.9±5.4 mm (ANOVA, p=.08). Effect size .31 for exercise intervention. Excluded VAS scores due to less than 75% completion of assessment. No patients showed reduction in pain ≥30% for either group.	"In conclusion, we report that the impact of an exercise program for a population of patients with peripheral NeP may increase exercise capacity, but failed to impact significantly upon pain severity and other comorbid conditions."	High dropout rate. Data suggest improved VAS scores in the exercise group but did not reach statistical significance.

Tricyclics/Tetracyclics

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Gilron 2009 (score = 7.0)	Tricyclics Amitriptyline & Nortriptyline	RCT	Sponsorship by the Canadian Institutes of Health Research. No mention of COI.	N = 56 patients 40 with diabetic polyneuropathy, 16 with postherpetic neuralgia.	Mean age: 63; 35 males, 21 females.	Gabapentin 3600 mg per day vs nortriptyline 100 mg vs Combined. 3600 mg	6 weeks, 12 weeks, 18 weeks	Daily Pain Intensity At max dose. Gabapentin 3.2 (p = 0.001) Nortriptyline 2.9 (p = 0.02) combined 2.3 percentage pain	"Combined gabapentin and nortriptyline seems to be more efficacious than either drug given alone for neuropathic pain,	Crossover trial Data suggest combination treatment nortriptyline and gabapentin better than

						Gabapentin, 100 mg Nortriptyline.		relief on treatment. Gabapentin 48.1% (p = 0.007) Nortriptyline 45.7% (p = 0.002) combined 68.4%. Average pain gabapentin 3.3 (p = 0.002) nortriptyline 3.1 (p 0.04) combined 2.5	therefore we recommend use of this combination in patients who show a partial response to either drug given alone and seek additional pain relief. Future trials should compare other combinations to their respective monotherapies for treatment of such pain."	either drug alone.
Kaur, 2011 (score=6.5)	Tricyclics Amitriptyline vs Duloxetine	RCT	No mention of sponsorship. No COI.	N = 58 patients with TII Diabetes and have experienced painful diabetic neuropathy (PDN) for at least 1 month.	Mean age of study participants: 52.5 Sex(M:F) 27:31	Amitriptyline group (N = 29) and duloxetine group (N = 29) received their respective treatment drug once daily for 6 weeks. A placebo washout period of 2 weeks was administered between the two treatments followed by a placebo run-out period of 4 weeks at the end of each treatment.	6 weeks	Results show a significant improvement in pain with both treatments compared to baseline values (P<0.001 for both groups). 55, 24, and 15% of patients in the amitriptyline group experienced pain relief compared to 59, 21 and 9% of patients in the duloxetine group. There was no significant difference in pain relief between groups.	"Both duloxetine and amitriptyline demonstrated similar efficacy in PDN. A large, multicentric clinical trial in other populations could possibly demonstrate the superiority of either drug."	Crossover trial, data suggest comparable efficacy.

Bowsher 1997 (score = 5.0)	Tricyclics Amitriptyline	RCT	Sponsorship by the Wellcome Foundation Ltd, and the Trustees of the Pain Relief Foundation. No mention of COI	N = 72 patients with herpes zoster.	Mean age: +60; 31 males, 49 females.	25 mg amitriptyline 1 daily for 90 days. vs placebo 1 daily for 90 days.	6 months.	Amitriptyline vs placebo pain free at 3 months 28 (73.7%) vs 21 (61.75%). Pain free at 6 months; 32 (84.2%) vs 24 (82.75%)	"This controlled trial suggests that low-dose amitriptyline (25 mg) can reduce the prevalence of PHN at 6 months after acute shingles by more than one-half."	Unclear regarding impact of acyclovir data suggest early treatment with low dose amitriptyline combined with acyclovir reduced pain associated with post-herpetic neuralgia
Watson 1998 (score = 5.0)	Tricyclics Amitriptyline & Nortriptyline	RCT	No mention of sponsorship or SOI.	N = 33 with postherpetic neuralgia.	No mention of mean age or sex.	5 weeks 10 mg increasing by 10 mg every 3-5 days. 2 week washout period and then crossover to other drug. (N = 33) Amitriptyline vs nortriptyline.	12 weeks.	VAS scores declined as time increased ($p < 0.0001$). 50% had equal good or poor response to AT or NT. 21 (67.7%) had at least a good response to AT or NT or both.	"We concluded that this study provides a scientific basis for an analgesic action of NT in PHN because pain relief occurred without an antidepressant effect, and that although there were fewer side effects with NT, AT and NT appear to have a similar analgesic action for most individuals"	Data suggest comparable efficacy between nortriptyline vs amitriptyline with fewer nortriptyline-related side effects.

Achar 2010 (Score = 5.0)	Tricyclics Amitriptyline	RCT	No mention of sponsorship or COI.	N = 45 with postherpetic neuralgia.	No mention of mean age. 30 males, 15 females.	Amitriptyine 25 mg once daily. (N = 15) vs Pregablin 75 mg twice daily. (N = 15) vs Combined same doses as above. (N = 15)	8 weeks	Differences at 4 weeks. (X^2 = 1.56, p > .05). Amitriptyline; ≥75% improvement 2 (13.4%), ≤75% improvement 13 (86.6%). Pregabalin; ≥75% improvement 8 (53.3%), ≤75% improvement 7 (46.7%). Combined; ≥75% improvement 11 (73.3%), ≤75% improvement 4 (26.7%). (X^2 = 11.23, (p < 0.05)).	"The present study demonstrates that the combination therapy is more efficacious in relieving pain, compared to monotherapy, in patients with PHN, at the end of eight weeks of treatment."	Data suggest combination therapy significantly reduces PHN pain.
Rowbatham2005 (score = 4.5)	Tricyclics – Desipramine vs Fluoxetine	RCT	Sponsored by NIH program project grants. No mention of COI.	N = 47 patients with postherpetic neuralgia.	Mean age: 72 years; 20 males, 27 females.	Desipramine group (DES N = 15) vs Amitriptyline group (AMI N = 17) vs Fluoxetine group (FLU N = 15). DES and AMI received 25 mg/day, then increased every 2-7 days, up to 150 mg/day. FLU received 20mg every other day, increased every 2-7 days, up to 60mg/day.	Follow-up at baseline one week before treatment and at 6 weeks of treatment.	There were no statistically significant results between groups in reduced percentage of VAS scores (pain intensity) comparing pretreatment to posttreatment (P = 0.12) or pain relief completing treatment before tapering (P = 0.15). Clinically significant results were see in reduction of VAS scores by 47% in	"Although the modified intent-to-treat analysis did not find the three antidepressants to be significantly different for the reduction in daily diary pain VAS or end-treatment pain relief category, desipramine produced the greatest reduction in pain intensity."	Data suggest comparable efficacy among groups with desipramine providing the best pain relief.

								DES, 38% in AMI, and 35% in FLU.		
Carasso 1979 (Score = 4.0)	Tricyclics Amitriptyline & Clomipramine	RCT	No mention of sponsorship or COI.	N = 67 suffering from trigeminal neuralgia, tension headache or post herpetic neuralgia.	Age range 35-70, no mention of mean age. 29 males, 38 females	Clomipramine; 20 mg to 75 mg daily (N = 35). Vs Amitriptyline; 30 mg to 110 mg daily (N = 32).	3 months	Trigeminal neuralgia improvement. the same clomipramine = 1 (11.1%), amitriptyline = 4 (44.4%). slight improvement 4 (11.1%) vs 2 (22.2%) moderate improvement 4 (44.1%) vs 1 (11.1%). Marked improvement 3 (33.3%) vs 2 (22.2%). Postherpetic pain improvement Clomipramine vs amitriptyline. Worse 1 (9.0%) vs 0. The same 3 (27.2%) vs 3 (30%) Slight improvement 4 (34.3%) vs 2 (20%) Moderate improvement 2 (18.2%) vs 3 (30%) Marked improvement 1 (9.0%) vs 2 (20%).	Treatment showed that clomipramine was better than amitriptyline in treating trigeminal neuralgia. Tended to be better in the treatment of tension headache. Amitriptyline is better in treating postherpetic neuralgia.	Relatively small sample. Data suggest clomipramine better for trigeminal neuralgia and amitriptyline better for postherpetic neuralgia after 3 months of treatment.
Watson 1982 (Score = 4.0)	Tricyclics Amitriptyline vs Placebo	RCT	No mention of sponsorship or COI.	N = 24 patients with typical severe postherpetic neuralgia for	Mean age: 66 years; 8 males, 16 females	Amitriptyline 12.5 to 25 mg every 2 to 5 days. For 3 weeks, washed	19 months.	Pain improvement. 16 of 24 patients, excellent, 6 poor, and 2 unchanged. ($p \leq 0.001$)	"We found that amitriptyline was superior to placebo in relieving	Crossover study small sample. Data suggest amitriptyline showed efficacy

				at least 3 months.		out for 1-2 weeks followed by 3 weeks of medication. Vs Placebo			postherpetic neuralgia."	in PHN patients over placebo.
Watson 1992 (Score = 4.0)	Tricyclics Amitriptyline & Maprotiline	RCT	Sponsorship by physicians' Services Incorporated (PSI). No mention of COI.	N = 35 patients with postherpetic neuralgia of more than 3 months.	Mean age: 71 years; 18 males, 17 females.	Amitriptyline for 5 weeks, 12.5 to 25 mg. Increased by 12.5 mg till pain managed. Vs Maprotiline for 5 weeks, 12.5 to 25 mg. Increased by 12.5 mg till pain managed.	5 weeks, 10 weeks.	VAS pain scale AT vs MT at 5 weeks ($p < 0.01$). 11 patients better outcome of AT vs MT. 12 similar. Of positive drug responses 21 of 32 were improved with AT (66%). 21 improved on MT.	"The findings of this study indicate that AT results in greater improvement in pain rating scales than MT and that it is clinically more effective for more patients than MT when side effects, disability, improvement in sleep, antidepressant effect and patient satisfaction are taken into account."	Crossover study Data suggest Maprotiline not as effective as Amitriptyline but both drugs had side effects.

SNRIs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hall, 2010 (score=7.0)	SNRIs Duloxetine	RCT	Sponsored by Eli Lilly and Company. COI, more than one of the authors have received or will receive benefits	N = 1139 patients with diabetic peripheral neuropathic pain (DPNP).	Mean age: 59.9 years; 647 males, 492 females.	Study 1 randomized patients to 20/mg/day, or 60mg/day or 60mg 2X/day of duloxetine, or	Follow-up at baseline, week 12, and 52, and at discontinua	In the 12 week phase and extension phase at 52 weeks, statistically significant results were seen in termination of	"The results of this pooled analysis of safety data from three studies in patients with DPNP demonstrate that duloxetine	Pooled analysis. Duloxetine 60 mg/day is generally well tolerated for management of diabetic

			for personal or professional use.			placebo for 12 weeks vs Study 2 and 3 with 60mg/day or 60mg 2X/day of duloxetine, or placebo for 12 weeks. Data were pooled to compare duloxetine n = 800, and placebo N = 339. An extension of these studies included these patients randomized into a 52 week 60mg 2X/day of duloxetine (N = 580), vs routine-care of nonmedicinal or medicinal therapy combinations (N = 287). All medication taken by mouth.	tion of patient.	treatment due to adverse events in the duloxetine patients compared to placebo (p < 0.001, and p = 0.007, respectively). For treatment-emergent adverse events (TEAE), there were significantly higher TEAEs for the duloxetine group compared to placebo for the 12 week phase (p < 0.001), and no significant difference of TEAE for the routine-care vs duloxetine in the extension phase. Main TEAEs were nausea, somnolence, and constipation.	treatment is relatively safe and well tolerated in both acute and extended dosing in this population…. Overall, there were low rates of discontinuation due to AEs, low incidence of cardiovascular or laboratory abnormalities and no worsening of neuropathy, nephropathy or retinopathy during long-term treatment with duloxetine."	peripheral neuropathic pain.
Kaur, 2011 (score=6.5)	SNRIs Duloxetine	RCT	No mention of sponsorship. No COI.	N = 58 patients with TII Diabetes and have experienced painful diabetic neuropathy (PDN) for at least 1 month.	Mean age of study participants: 52.5 Sex(M:F) 27:31	Amitriptyline group (N = 29) and duloxetine group (N = 29) received their respective treatment drug once daily for 6 weeks. A placebo	6 weeks	Results show a significant improvement in pain with both treatments compared to baseline values (P<0.001 for both groups). 55, 24, and 15% of patients in	"Both duloxetine and amitriptyline demonstrated similar efficacy in PDN. A large, multicentric clinical trial in other populations could possibly demonstrate the	Crossover trial, data suggest comparable efficacy.

						washout period of 2 weeks was administered between the two treatments followed by a placebo run-out period of 4 weeks at the end of each treatment.		the amitriptyline group experienced pain relief compared to 59, 21 and 9% of patients in the duloxetine group. There was no significant difference in pain relief between groups.	superiority of either drug."	
Sindrup, 2003 (score=6.0)	SNRIs Venlafaxine	RCT	No mention of COI and sponsored by Danish National Research Council (NASTRA grant no. 42820) and the local research foundation at Odense University Hospital. Study medication provided by Wyeth Lederle and Nycomed.	N=40 patients with polyneuropathy	Mean age: 56 years; 23 males, 9 females	Venlafaxine: 37.5 mg b.i.d. in the first week, 75 mg b.i.d. the second week, and 112.5 mg b.i.d for the remaining 2 weeks vs Imipramine: 25 mg b.i.d. in the first week, 50 mg b.i.d. the second week, and 75 mg b.i.d. for the remaining 2 weeks vs Placebo: dosed similarly in the placebo phase and the treatment	4 weeks	Relative measure of total pain difference significant (p=0.0011). Lower pain score was observed for venlafaxine (p=0.004, Bonferroni-corrected significance p=0.017). Pain scores were lower on imipramine than placebo (p=0.0005).	"Venlafaxine relieves pain in polyneuropathy and may be as effective as imipramine."	Crossover trial. Data suggest venlafaxine effexor decreases polyneuropathic pain but may be a little less efficacious than imipramine.

						periods as necessary to keep blinding according to the double dummy technique				
Kajdasz, 2007 (score=5.5)	SNRIs Duloxetine	Post hoc RCT	No mention of sponsorship. COI, more than one of the authors have received or will receive benefits for personal or professional use from Eli Lilly and Company.	N = 1024 patients with diabetic peripheral neuropathic pain (DPNP).	Mean age: 59.9 years; 572 males, 452 females.	Three studies were pooled together and divided between group 1: duloxetine 60mg/day (N = 344), vs duloxetine 60mg2X/day (N = 341), vs placebo (N = 339). All medication taken by mouth for 12 weeks.	Follow-up at baseline, 12 weeks, and patient discontinuation.	Results are reported of number needed to treat (NNT) and number needed to harm (NNH) with a 95% CI based on weekly average scores of 24-hour pain severity scores. Sixty mg/day of duloxetine had NNTS of 5.2 on last observation carried forward (LOCF), and 5.3 for baseline observations carried forward (BOCF). NNHs were 17.5 due to adverse events (AE) that caused discontinuation. Sixty mg 2X/day had NNTs of 4.9 at LOCF and 5.7 at BOCF. NNHs were 8.8 due to AE that caused discontinuation.	"These post hoc results of 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group trials suggest that duloxetine was effective and well tolerated for the management of these patients with painful polyneuropathy, including DPNP."	Post-hoc pooled analysis (combo of 3 RCTs). Data suggest duloxetine shows efficacy in the management of diabetic peripheral neuropathic pain.
Wernicke, 2007 (score=4.5)	SNRIs Duloxetine	RCT	No mention of sponsorship or COI.	N = 293 patients with diabetic	Mean age: 58.3 years; 135 males,	After 12 week trial, groups were	Follow-up at baseline,	There were no significant difference between	"In summary, the present results provide evidence	Open label extension trial. Routine care

				peripheral neuropathic pain (DPNP).	158 females.	randomized into duloxetine group of 60mg 2X/day (N = 197) vs routine care (N = 96) of medicinal and nonmedicinal interventions.	12 and 65 weeks.	groups in serious adverse events (SAEs), discontinuations due to adverse events, diabetic complication assessments, vital signs, or in number of treatment-emergent adverse events (TEAEs). However, duloxetine group had more TEAEs of asthenia than the routine-care group (p=0.018). Significant differences between groups was in the SF-36 health outcomes favoring the duloxetine group for better scores in mental health, physical components, physical functioning (all P < 0.05), bodily pain, and vitality (all P < 0.01).	that duloxetine has significant advantages on some health outcome measures, and appears to be safe for long-term therapy of patients with DPNP without significant psychiatric or medical comorbidities."	bias. Population included both Type 1 and Type 2 diabetes. Duloxetine appears to be a safe treatment tool for DPNP.
Bouhassira, 2014 (score=4.0)	SNRIs Duloxetine	Post Hoc RCT	Sponsored by Eli Lilly & Company. More than one of the authors have received or will receive benefits	N = 790 patients with diabetic peripheral neuropathic pain (DPNP).	Mean age: 61.6 years; 442 males, 348 females.	In the initial therapy period of 8 weeks, Cluster 1a, 2a, 3a of 60mg of duloxetine/day	Follow-up at baseline, 4, 8, 12, and 16 weeks.	Three clusters were formed based on similar Neuropathic Pain Symptom Inventory (NPSI) responses. In the	"The present exploratory analyses further support the hypothesis that variability in	Data suggest 3 different pain profile groups via NPSI phenotyping witch may assist

			for personal or professional use from Eli Lilly & Company.			groups (N=112, N=154, N=132 respectively), vs Cluster 1b, 2b, 3b 300mg of Pregabalin/day groups (N=120, N=126, N=146). In the 2nd therapy period of 8 weeks, cluster 1a, 2a, 3a combination therapy of 60 mg duloxetine and 300 mg pregabalin/day (N=50, N=68, M=48), vs cluster 2a, 2b, 2c monotherapy of 120mg duloxetine or 600 mg of pregabalin (N=54, N=62, N=52).		initial 8 week therapy period, significant results were seen in reduced Brief Pain Inventory (BPI) scores in cluster 2 and 3 for duloxetine (p=0.020, p=0.002 respectively). In the 2nd 8 week therapy period, there were no statistically significant difference between clusters 1 2 or 3 (p=0.090, p=0.107, p=0.310 respectively).	sensory profiles exists across patients with diabetic peripheral neuropathic pain. In essence, the identification of subgroups of patients with distinct pain characteristics at baseline and their differential responses to duloxetine and pregabalin, alone or in combination, is encouraging, and indicates that heterogeneity in the patient population should be taken into account for a more stratified or even personalized treatment approach."	in individualized treatment plans regarding the dosing of both duloxetine and pregabalin.

SSRIs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Otto, 2008 (score=6.5)	SSRIs Escitalopram	RCT	Sponsored by unrestricted grants from H. Lundbeck A/S and Gruenenthal	N=41 patients with polyneuropathy	Mean age: 62 years; 29 males, 12 females	Escitalopram group vs placebo group	5 weeks	Escitalopram group observed higher pain relief after treatment compared to	"This study found a pain-relieving effect of escitalopram in patients with	Crossover study. Data suggest a modest clinically relevant effect

			GmbH and a grant from the Danish Clinical Intervention Research Academy.					placebo (p=0.001). All scales of SF-36 and sum-score of MDI were unchanged by escitalopram compared to placebo (SF-36: p=0.086-0.973; MDI: p=0.812).	painful polyneuropathy, but a clinically relevant effect was obtained in only few patients. Currently, the drug cannot be recommended as a standard treatment in neuropathic pain."	of escitalopram for PN pain.
Brasch-Andersen, 2011 (score=5.5)	SSRIs Escitalopram	RCT	No mention of COI or sponsorship.	N=34 participants from peripheral neuropathic pain study	Mean age: No mention of age; 26 males, 8 females	All patients received 6 weeks of escitalopram (20 mg/day) and placebo for 6 weeks and randomized between the two groups.	None	SNP in serotonin receptor 2A showed tendency (p=0.11 of A allele carriers exhibiting better response with treatment than wild type allele (56% to 24%). Carriers of C allele at rs6318 observed better pain relief with escitalopram (15.5 fold increase) compared to G allele (OR 15.5, p=0.014). Better relief was also observed for 5-HTTLPR polymorphism with increasing number of short alleles (OR 5.7, p=0.057).	"This study indicates that variation in the HTR2C gene is associated to the pain-relieving effect of escitalopram in patients with painful polyneuropathy."	Data suggest variations in the HTR2C gene is correlated to pain reduction in Escitalopram.
Semenchuk, 2001 (score=5.0)	SSRIs	RCT	Sponsored by a grant from GlaxoWellcome, a	N = 41 with neuropathic pain for at	Mean age: 60 years;	Treatment of 150 mg of Bupropion SR (n	12 weeks	Mean average pain intensity diary scores during week	"[B]upropion SR (150–300 mg daily) was effective and	Data suggest bupropion SR (150 mg-300 mg

	Bupropion		division of GlaxoSmithKline. No mention of COI.	least 3 months.	19 males, 22 females	= 19) vs placebo (n = 22)		6, a within-patient comparison, favored bupropion SR (P < 0.001; two-tailed t-test). No differences seen in between-patient comparison. Bupropion SR was effective at week 2 (P < 0.05; paired, two-tailed t-test) and pain continued to decrease during the next 4 weeks. Most patients initially receiving placebo had no relief until the cross-over period.	well tolerated for the treatment of neuropathic pain."	daily) efficacy may be appropriate for NP pain treatment.
Arnold, 2008 (score=5.0)	SSRIs Mirtazapine	Experimental Study	No sponsorship or COI.	N=10 healthy patients	Mean age: 40.6±7.6 years; 5 males, 5 females.	MTZ group vs Placebo group	None	Minimal intensity of stimulation (IST) for upper limb necessary to elicit the NFR was 176±82 mV for placebo, and 228±70 mV for MTZ (29% increase, p<.006). For lower limb, IST was 192±59 for placebo and 210±87 on drug.	"We observed a MTZ-induced increase in the pain tolerance (ie, pain relief) in healthy human participants. Considering its excellent risk and side effects profile, 7 further studies are needed to assess whether an effect against chronic neuropathic pain can be obtained and thus whether MTZ could be an	Crossover study, small sample, sparse methods. Data suggest Mirtazapine may improve pain tolerance and sleep quality.

									alternative to TCA. Moreover, NFR threshold evaluation is well tolerated and seems to be a safe, and a useful technique to select new molecules that may decrease pain. It might also be a useful additional tool for the treatment of neuropathic pain patients."	
Rowbatham 2005 (score = 4.5)	SSRIs Fluoxetine vs Desipramine	RCT	Sponsored by NIH program project grants. No mention of COI.	N = 47 patients with postherpetic neuralgia.	Mean age: 72 years; 20 males, 27 females.	Desipramine group (DES N = 15) vs Amitriptyline group (AMI N = 17) vs Fluoxetine group (FLU N = 15). DES and AMI received 25 mg/day, then increased every 2-7 days, up to 150 mg/day. FLU received 20mg every other day, increased every 2-7 days, up to 60mg/day.	Follow-up at baseline one week before treatment and at 6 weeks of treatment.	There were no statistically significant results between groups in reduced percentage of VAS scores (pain intensity) comparing pretreatment to posttreatment (P = 0.12) or pain relief completing treatment before tapering (P = 0.15). Clinically significant results were see in reduction of VAS scores by 47% in DES, 38% in AMI, and 35% in FLU.	"Although the modified intent-to-treat analysis did not find the three antidepressants to be significantly different for the reduction in daily diary pain VAS or end-treatment pain relief category, desipramine produced the greatest reduction in pain intensity."	Data suggest comparable efficacy among groups with desipramine providing the best pain relief.

Anticonvulsants

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Vinik 2007 (score = 8.5)	Anticonvulsants Lamotrigine vs Placebo	RCT (Two identical high quality RCTs with one report)	Funded by GlaxoSmithKline. No mention of COI.	N = 720 with painful diabetic neuropathy	Mean age is 59.9 years. 392 males, 400 females.	Lamotrigine 200mg vs. 300mg vs. 400mg vs. placebo. Study protocol included 7-week dose escalation phase and 12-week constant dose phase; 200mg dose was not statistically different from placebo.	Follow up at 19 weeks.	Graphic representations suggest dose-response relationships.	"In a post hoc analysis of pooled data including only patients who reached their target dose, lamotrigine 400mg conferred greater (p ≤0.05) mean reduction in pain-intensity score from baseline to week 19 than placebo (-2.5 for 300mg and -2.7 for 400mg vs. -2.0 for placebo)."	Lack of much separation between 300mg and 400mg doses and higher adverse effects in 400mg group suggest 300mg may be optimal dose for many patients.
Silver 2007 (score = 8.5)	Anticonvulsants Lamotrigine	RCT	Funded by GlaxoSmithKline. No mention of COI.	N = 223 with neuropathic pain already taking gabapentin	Mean age is 60.2 years. 132 males, 91 females.	Flexible dose of lamotrigine 200mg/300mg/ 40mg vs. placebo. Doses gradually escalated.	Follow up at 14 and 19 weeks.	Pain intensity scores declined from 6.3 to 4.2 for placebo, and 6.5 to 4.4 (not significant) for lamotrigine. Withdrawals greater in lamotrigine group (24% vs. 11%); side effects primarily rash (18% vs. 13%), dizziness (9% vs. 10%) or somnolence (6% vs. 2%).	"Lamotrigine (up to 400mg a day) added to gabapentin, a tricyclic anti-depressant , or a non-opioid analgesic did not demonstrate efficacy as an adjunctive treatment of neuropathic pain but was generally safe and well tolerated."	Diagnoses included diabetic neuropathy, postherpetic neuralgia, traumatic or surgical nerve injury, incomplete spinal cord injury, trigeminal neuralgia, multiple sclerosis and HIV neuropathy.

Raskin 2004 (score = 8.0)	Anticonvulsants Topiramate vs Placebo	RCT	Supported by a grant from Ortho-McNeil Pharmaceutical, Inc. N.R.R., D.J.H., D.M.J., and J.X. are employees of Ortho-McNeil Pharmaceutical, Inc. Each has equity ownership interest in excess of $10,000. A.I.V. has received grants and honoraria in excess of $10,000 from Ortho-McNeil Pharmaceutical, Inc.	N = 323 with painful diabetic neuropathy	Mean age is 59.2 years. 157 males, 160 females.	Topiramate (N = 208) titrated to 400mg a day or maximum tolerated dose over 8 weeks vs. placebo (N = 109); 4-week maintenance period.	Follow up at 4, 8, and 12 weeks.	Topiramate resulted in statistically significantly lower scores at final visit (68.0 to 46.2mm) vs. placebo (69.1 to 54.0mm). Sleep disruption improved more in topiramate group.	Authors concluded that topiramate monotherapy reduced pain and body weight more effectively than placebo.	Dropout rates 47.7% topiramate; 26.6% placebo, mostly due to adverse effects (GI and CNS-related), and appear to affect interpretation of results.
Thienel 2004 (score = 8.0)	Anticonvulsants Topiramate vs Placebo	RCT (One report of 3 high-quality RCTs)	Supported by Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ, USA. No mention of sponsorship.	N = 1,269 with diabetic neuropathy	Mean age is 58.3 years. 734 males, 535 females.	Placebo N = 384 vs. topiramate. N = 885. Doses differed (placebo, 100/200/400mg a day; placebo, 200/400mg a day; and placebo, 100/200mg a day).	Follow up at 12 weeks.	After a 28-day treatment phase, there was a titration phase of 6-10 weeks and then a stable dose phase of 12 weeks. Dropouts ranged from 37% to 62%.	These studies did not find "topiramate to be significantly more effective than placebo in reducing pain scores."	Differences in doses between trials makes interpretation difficult. Pooled analyses makes analyzing results difficult; score may overstate true quality.
Holbech, 2011 (score=7.5)	Anticonvulsants	RCT	No COI and sponsored by UCB Pharma that	N=35 patients with painful	Mean age: 57 years;	Levetiracetam group: received up to 3000 mg/d	12 weeks	Main pain relief with levetiracetam was 2.29±1.13 and	"This study indicates that the anticonvulsant	Crossover design. Data

	Levetiracetam vs Placebo		provided study drug and GCP-monitor unit.	polyneuropathy	22 males, 13 females	for a 6 week period vs Placebo group: received similar protocol with placebo		2.28±1.19 with placebo (p=0.979).	levetiracetam has no clinically relevant effect on painful polyneuropathy."	suggest lack of efficacy.
Eisenberg 2001 (score = 7.0)	Anticonvulsants Lamotrigine vs Placebo	RCT	Supported by Glaxo-Wellcome, Park, NC. No mention of COI.	N = 53 with painful diabetic neuropathy	Mean age is 55.3 years. 33 males, 20 females.	Lamotrigine (N = 27) vs. placebo (N = 26). Dose gradually titrated.	Follow up at 8 and 10 weeks.	Pain intensity decreased from 6.4±0.1 to 4.2±0.1 vs. from 6.5±01 to 5.3±0.1 for placebo. Statistically significant at 200mg, 300mg, and 400mg. Did not appear to be a dose response relationship in data, suggesting patients generally required 200 to 400mg; 10% of placebo vs. 32% of lamotrigine felt medication highly efficacious.	"Lamotrigine is effective and safe in relieving the pain associated with diabetic neuropathy."	Long-term efficacy and safety is not established by this small scale study. Study showed no increased adverse events in the lamotrigine group (17 vs. 21). Despite randomization, duration of diabetes longer in treatment group.
Smith, 2013 (score=6.0)	Anticonvulsants Carisbamate vs Placebo	RCT	Sponsored by Janssen Research & Development, LLC, Raritan, N.J., U.S.A. Dr. Smith's employer received compensation from Janssen Research & Development	N=386 patients with painful diabetic neuralgia or post herpetic neuropathy.	Mean age: 58±8.94 years; 225 males, 161 females	Study 1&2: Patients received carisbamate 400 mg/day or placebo for 4 weeks vs Study 3: received either 800 mg/day, 1200 mg/day, pregabalin 300 mg/day, or	8 weeks, 15 weeks	Square mean differences between carisbamate and placebo groups were study 1: -0.512 carisbamate 400 mg/day; study 2: -0.307 carisbamate 400 mg/day; and study 3: -0.51 carisbamate 800 mg/day; -0.55 carisbamate 1200	"Carisbamate, although well tolerated, did not demonstrate efficacy in neuropathic pain across these studies, nor did the active comparator pregabalin"	Pooled analysis from 3 RCTs. Data suggest comparable in efficacy between all gro ups.

			for study conduction.			placebo for 15 weeks		mg/day; and -0.43 pregabalin 300 mg/day. Neither caribamate nor pregabalin differed from placebo for all 3 studies.		
Otto, 2004 (score=6.0)	Anticonvulsants Valproic acid vs Placebo	RCT	No mention of COI or sponsorship.	N=31 patients with painful polyneuropathy	Mean age: 60 years; 19 males, 12 females	Valproic Acid group: received 300 mg vs Placebo group	8 weeks	Compliance was confirmed by serum drug concentrations (median, 462 mmol; range, 226.8 to 810.6 mmol). Carryover (p = 0.32 to 0.91) and period effects (p = 0.07 to 0.74) were not present for the primary effect variable or individual rating of pain symptoms.	"This study found no effect of valproic acid on pain in polyneuropathy for the total population of patients and relevant subgroups."	Crossover trial, data suggest lack of efficacy of valproic acid for PN pain.
Harke 2001 (score = 6.0)	Anticonvulsants Carbamazepine vs Placebo	Placebo-controlled Trial (Two active phases)	No mention of sponsorship or COI.	N = 43 with peripheral neuropathic pain with implanted SCS and prior documented response of "permanent pain relief without any pain medication" for neuropathic pain included	Mean age is 55 years. 21 males, 34 females.	Compared carbamazepine (CMZ, 200mg TID) with placebo in Phase I, and sustained-release morphine (30mg TID) vs. placebo in Phase II. In Phase I, patients randomly allocated to receive 600mg a day CMZ (n = 22) or placebo (n =	Follow up at 37 days.	Forty adverse drug reactions (ADRs) in CMZ vs. 5 in placebo; 5/22 CMZ vs. 3/21 placebo switched on SCS within 4 hours (non-responders). Phase II: after CMZ elimination interval of 7 days, 38 had sustained-release morphine (90mg a day, n = 21) or placebo (n = 17) for 8 days; 8/36	"CMZ is effective in peripheral neuropathic pain. Morphine requires larger individually titrated dosages than those used in this study for results to be adequately interpreted."	Population heterogeneous with multiple conditions, yet compiled with high degree of selection, thus applicability outside of this set of patients unclear. Higher non-responder rates with active medication vs. placebo in both trials, despite

				in Phase I (36 later entered Phase II); included those with recurrence of pain with SCS		21) during SCS period of 6 days, then SCS switched off for up to 8 days. Protocol labeled those who could switch off SCS permanently as responders, those who could overcome upper limit of 425 minutes as partial responders, and remainder as non-responders.		required dose reductions due to nausea, dizziness, vomiting; 20 ADRs a day in morphine vs. 2 in placebo. Six in morphine vs. 4 in placebo switched on SCS within 4 hours (non-responders). In 38 who completed Phase 1, significant delay in pain increase with CMZ vs. placebo. Phase II: 2 CMZ, 1 morphine complete pain relief and continued medication; 35 returned to SCS.		preselection. Suggests that larger studies with single diagnostic entity are required to clarify diagnostic-specific response rates.
Grosskopf 2006 (score = 6.0)	Anticonvulsants Oxycarbazepine vs Placebo	RCT	Funded by Novartis Pharmaceuticals Inc. No mention of COI.	N = 141 with painful diabetic neuropathy	Mean age is 61.6 years. 55 males, 86 females.	Oxcarbazepine (N = 71) vs. placebo (N = 70). Dose initiated and titrated over 4 weeks.	16 weeks	Percentage reductions in VAS scores were 27.9% in oxcarbazepine vs. 31.1% in placebo group.	Authors found "no statistically significant difference in therapeutic effect… between oxcarbazepine (1,200mg a day) and placebo."	Few results presented. Dropouts quite high (40.8% vs. 24.3% placebo) which may have affected results.
Kochar, 2005 (score=5.0)	Anticonvulsants Divalproex sodium vs Placebo	RCT	No mention of COI or sponsorship.	N=40 patients with post-herpetic neuralgia	Mean age: 57.24 years; 22 males, 18 females	Group A (n=22): received divalproex sodium vs Group B (n=18): received placebo	2, 4, 8 weeks	Group A showed reduction in pain: SF-MPQ, 20.47±2.29 to 11.90± 6.52 (p<0.0001); PPI 4.0±0.52 to 1.95_1.29 (p<	"Divalproex sodium provides significant pain relief in patients of post-herpetic neuralgia, with very little incidence of adverse reactions. These data provide	Data suggest after 8 weeks of divalproex treatment pain scores were significantly improved (reduced).

								0.0001); VAS 70.17±9.21 to 31.27±29.74 (p< 0.0001) and 11 PLS 6.97±0.73 to 3.63±2.34 (p<0.0001) compared to Group B. Questionnaire showed improvement of 58.2% with Group A treatment vs Group B 14.8%.	a basis for longer trials in a larger group of patients."	
Irizarry, 2009 (score=4.5)	Anticonvulsants Lamotrigine vs Placebo	RCT	Sponsored by GlaxoSmithKline. No mention of COI.	N=826 patients with neuropathic pain	Mean age: 60.04 years; 433 males, 393 females	Pooled lamotrigine treatment (n=574) vs Pooled Placebo Arms (n=252):	12 weeks	Higher baseline PI-NRS showed association with greater improved pain score at 12 weeks. Change score declined by 0.38 (ie, ΔPI-NRS= -0.38 per unit increase in baseline PI-NRS, r2=0.06, P<0.001).	"These results suggest that both patient and study site characteristics can influence the response in the placebo arms of neuropathic pain studies."	Pooled Analysis, Data suggest study site as well as patient characteristics may influence and/or increase the placebo response.
Beydoun 2006 (score = 4.0)	Anticonvulsants Oxycarbazepine vs Placebo	RCT	No mention of sponsorship or COI.	Total N = 594. N = 497 for study 1 and N = 97 for Study 2 with painful diabetic neuropathy	Mean age is 59 years.253 males, 341 females.	Oxcarbazepine vs. placebo. (Report contains two studies with initial study an open-label study (only double-	2 weeks.	Patients titrated in open-label phase over 4 weeks up to 900mg BID. Adverse effects high: 93.8% in open-label phase had at least 1	Authors concluded that "long-term treatment with oxcarbazepine is generally well tolerated in patients with	Medication may be useful, but considerable adverse effects to overcome. Detailed results on health

						blind RCT is reviewed here.)		adverse effect (dizziness (59.6%), somnolence (36.4%), headache (26.6%), nausea (26.0%) and vomiting (20.9%). Hyponatremia occurred in 8 patients (3.8%) and 5 necessitated discontinuation.	painful diabetic neuropathy."	outcomes such as pain ratings in RCT arm sparse. The 12-month treatment phase for open-label phase among 497 patients is a strength for ascertaining adverse effects and safety.

Gabapentin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Backonja 1998 (score = 10.0)	Gabapentin	RCT	Sponsored by Parke-Davis. No mention of COI.	N = 165 with painful diabetic neuropathy	Mean age is 53 years. 99 males, 66 females.	Gabapentin 900mg a day in Week 1, 1,800mg a day in Week 2, 2400mg a day in Week 3, 3,600mg in Week 4 with second 4 weeks of trial on a stable dose (n = 84) vs. placebo (n = 81) for 8 weeks.	Follow up at 8 weeks.	Mean pain scores (baseline/end point): gabapentin (6.4/3.9) vs. placebo (6.5/5.1), p <0.001. Data suggest that effects may not have been fully realized within 8-week treatment timeframe.	"At doses of 1800 to 3600 mg/d, gabapentin was effective and well tolerated in the treatment of adults with neuropathic pain."	Adverse effects included dizziness, somnolence, and confusion. Data suggest some efficacy.
Chandra, 2006	Gabapentin	RCT	Sponsored by Pfizer. No mention of COI.	N= 76 patients with postherpetic neuralgia.	Mean age: 54.05 years; 34	Nortriptyline (n=38) – patients given nortriptyline	No follow up.	The difference between baseline and week 8 in pain score (Likert Scale)	"Gabapentin was shown to be equally efficacious but was better	Data shows comparable efficacy between

(score=7.0)					males, 44 females.	25 mg thrice a day at 2 weeks and 25 mg – 2 thrice a day at 4 weeks, respectively for an 8 week treatment period. Vs. Gabapentin (n=38) – patients were given 300 mg × 2 thrice at 2 weeks and 300 mg × 3 thrice at 4 weeks, respectively for a 8 week treatment period.		mean score for nortriptyline was 2.18 and for gabapentin was 1.97, p=0.62. The VAS score for nortriptyline was 2.37 and for gabapentin was 2.00, p=0.47.	tolerated compared to nortriptyline and can be considered a suitable alternative for the treatment of PHN."	gabapentin and nortriptyline but gabapentin was better tolerated.
Rice, 2001 (score=6.5)	Gabapentin	RCT	Sponsored by Pfizer Ltd. A.S.C.R. was paid a consultancy fee for his independent help and advice on this project, by Pfizer.	N=334 patients with postherpetic neuralgia.	Mean age: 75.32 years; 138 males, 196 females.	Placebo (n=111) – Patients took the same number of capsules as those assigned to gabapentin. Vs. Gabapentin 1800 mg/day (n=115) – after 1	1 month.	The change in average daily pain score form baseline week to final study week for placebo group was 6.4 vs. 5.3 (15.7% reduction), for the gabapentin 1800 mg group was 6.5 vs. 4.3 (34.5% reduction, and for the gabapentin 2400 mg group was	"In conclusion, this study adds to the growing evidence that gabapentin significantly reduces chronic neuropathic pain resulting from postherpetic neuralgia, reduces sleep interference and improves some domains of	Data suggests gabapentin decreases PHN associated pain and may have fewer side effects than tricyclics.

						week on treatment, the dose was titrated up to 1800 mg/day (1500 mg/day on day 8 and 1800 mg/day on days 9–14) Vs. Gabapentin 2400 mg/day (n=108) – after 2 weeks, patients had their dose titrated up to (2100 mg/day on day 15 and 2400 mg/day from day 16 onwards). All patients received their medication 3 times a day, daily for 7 weeks.		6.5 vs. 4.2 (34.4% reduction. Difference between placebo and gabapentin 1800 mg: 18% (95% CI 10.9–26.8%; P<0.01); between placebo and gabapentin 2400 mg: 18.7% (95% CI 10.7–26.7%; P<0.01).	quality of life." "Thus, this study confirms the role of gabapentin as an efficacious and well-tolerated treatment for postherpetic neuralgia."	
Levendoğlu, 2004 (score=6.0)	Gabapentin	RCT	No sponsorship. No mention of COI.	N = 20 paraplegic patients with complete traumatic spinal cord	Mean age: 35.9 years; 13 males, 7 females.	Group A or GBP treated group (N = 10) vs	No follow up.	VAS scores show significant difference between the GBP-treated group and placebo group at all times (p	"Gabapentin can be added to the list of first-line medications for the treatment of chronic	Crossover design. Data suggest significant pain reduction over 8 weeks.

				injury and neuropathic pain.		Group B or placebo control group (N = 10). Doses for both group Doses for both groups: week 1, 900 mg/day; week 2, 1800 mg/day; week 3, 2400 mg/day; and week 4, 3600 mg/day.		< 0.001). Baseline VAS scores show no changes at 8 weeks, ($p < 0.05$).	neuropathic pain in spinal cord injury patients. It is a promising new agent and offers advantages over currently available treatments."	
Parsons, 2004 (score=6.0)	Gabapentin	RCT	No mention of sponsorship or COI.	N=603 patients with postherpetic neuralgia.	Mean age: 72.7 years; 274 males, 441 females.	Placebo (n=245) – patients were given a placebo drug for 7-8 weeks. Vs. Gabapentin <1800 mg/d (n=358) – Gabapentin was initiated at 300 mg/d and titrated to maintenance doses of 1800 by day 12 to 24. Vs. Gabapentin ≥1800 mg/d	No follow up.	Patients receiving gabapentin <1800 mg/d reported dizziness significantly more often than those receiving placebo (20.2% vs 7.4%, respectively; P < 0.002). The incidence of somnolence at lower doses was significantly greater than that with placebo (5.8%) ($p < 0.001$). There was a higher incidence of peripheral edema with gabapentin ≥1800 mg/d compared with gabapentin <1800	"In this pooled analysis of adverse-event data from 3 clinical trials in patients with PHN, the incidence of peripheral edema was increased when gabapentin was titrated to ≥1800 mg/d. Dizziness and somnolence, the other most commonly occurring adverse events, were transient and did not occur more frequently or worsen with titration to ≥1800 mg/d. Based on	Pooled analysis. Data suggest dosing of gabapentin should include consideration of adverse events such as peripheral edema at highest doses (≥1800 mg/d).

						(n=321) – Gabapentin was initiated at 300 mg/d and titrated to maintenance doses of 1800 to 3600 mg/d by day 12 to 24.		mg/d (7.5% vs 1.4%, respectively).	these findings, it does not appear that safety concerns should limit titration of gabapentin to achieve optimal efficacy."	
Gordh, 2007 (score=6.0)	Gabapentin	RCT	No mention of sponsorship or COI.	N=120 patients with traumatic nerve injury induced neuropathic pain.	Mean age: 48.8; 56 males, 64 females.	Gabapentin-placebo (n=61) – titration of gabapentin started with 300 mg and increased till 2400 mg daily for five weeks, a washout period for 2 weeks, and patients received the placebo daily for five weeks. Vs. Placebo-gabapentin (n=59) - patients received the placebo daily for five weeks, a washout period of 2 weeks, titration of gabapentin started with 300 mg and increased till	No follow up.	The mean VAS pain intensity score for the gabapentin-placebo group and placebo-gabapentin group in the first treatment period at baseline was 52.2 and 54.1, respectively; at week 5 was 45.2 and 47.1. When compared the baseline to week 5 VAS score was 7.2 and 6.9 respective to G-P and P-G groups. In the second treatment period, the G-P and P-G groups reported VAS score at week 8 (50.9 and 52.6, respectively), at week 13 (49.9 and 47.2), and comparing week 8 and week 13 (0.5 and 5.1). More patients reported that the pain had	"Gabapentin was well tolerated. The most common adverse effects were dizziness and tiredness."	Data suggest a significant pain relief response in gabapentin group.

						2400 mg daily for five weeks.		subsided by half during gabapentin treatment (n = 22) than during placebo treatment (n = 8) (p = 0.012)		
Rowbotham, 1998 (score=6.0)	Gabapentin	RCT	Sponsored by Parke-Davis. Dr. Magnus-Miller and Ms. Bernstein are employees of Parke-Davis, Division of Warner-Lambert Co, and own stock and hold options to purchase further stock in the company.	N= 229 patients with postherpetic neuralgia.	Mean age: 72.2 years; 118 males, 107 females.	Gabapentin (n=113) – patients began with an initial does of 300 mg/d and 4-week titration till 3600 mg/d for a total of 8-week treatment period. Vs. Placebo (n=116) – Patients received placebo tablets similarly to gabapentin for 8 weeks.	No follow up.	Change from baseline in average daily pain score for placebo and gabapentin at week 2 was -0.2 and -1.6 (p<0.001), respectively; at week 4 was -0.3 and -2.0 (p<0.001); at week 8 was -0.5 and -2.1 (p<0.001). Subjects receiving gabapentin had a reduction in daily pain score from 6.3 to 4.2 compared to placebo group, which reduced from 6.5 to 6.0 points (p<0.001).	"Gabapentin is effective in the treatment of pain and sleep interference associated with PHN. Mood and quality of life also improve with gabapentin therapy."	Data suggests significant pain relief scores in gabapentin group.
Gilron, 2005 (score=5.5)	Gabapentin	RCT	Sponsored by the Canadian Institutes of Health Research (CIHR). Dr. Gilron reports having served on paid advisory	N=57 patients with diabetic neuropathy or postherpetic neuralgia.	Mean age: 63.1 years; 32 males, 25 females.	Morphine (n=16) – patients received a dose of 120 mg of morphine daily for five weeks. Vs. Gabapentin (n=13) – patients	No follow up.	The mean daily pain at a maximal tolerated dose of the study drug was as follows: 5.72 at baseline, 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine, and 3.06 with the gabapentin–	"Gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent, with constipation, sedation, and dry mouth as the most	4 period crossover trial. Data suggests a combination of gabapentin with morphine results in enhanced analgesia (better efficacy) with lower doses of

			boards for Pfizer during the past two years. Dr. Houlden reports having received grant support for research from Pfizer and Aventis-Pharma for other studies during the past two years.			received a daily dose of 3200 mg gabapentin for five weeks. Vs. Morphine and gabapentin (n=14) – patients received a daily dose of 60 mg morphine and 2400 mg gabapentin for five weeks. Vs. Placebo (n=14) – patients received a daily dose of 1.6 mg Lorazepam for five weeks.		morphine combination (P<0.05 for the combination vs. placebo, gabapentin, and morphine).	frequent adverse effects."	each drug compared to the individual drug doses given alone.
Yelland, 2009 (score=5.5)	Gabapentin	RCT	Sponsored by the Australian Health Ministers Advisory Council. No COI.	N=55 patients with neuropathic pain.	Mean age: 57.6 years; 30 males, 43 females.	3 comparisons of 2-week periods on gabapentin and placebo (n=48) Gabapentin– patients received 600-1800 mg/d of gabapentin for 2 weeks. Vs.	No follow up.	Within the population that completed at least one cycle, the response to gabapentin was better than placebo in 16 participants. No difference was shown in 38 (69%), and 1 (2%) showed a better response to placebo.	"The response rate and mean reduction in symptoms with gabapentin were small. Gabapentin prescribing post trial was significantly influenced by the trial results.'	Pooled N-of-1 randomized analysis with high dropout rate with different amounts of drug consumed by participants with differing numbers of cycles.

						Placebo – patients received placebo for 2 weeks.				
Extended Release Gabapentin										
Wallace, 2010 (score=6.5)	Extended Release Gabapentin	RCT	Sponsored by Depomed Inc. MSW has received research support from Depomed. Inc. GI has participated in advisory boards for Eli Lilly. Elan. Neurogesx and Depomed. and in speaker bureaus for Eli Lilly. Pfizer. Elan and Primera. VEC is an employee of Depomed, Inc. and owns stock and holds options for Depomed, Inc. Editorial assistance was	N=407 patients with post-herpetic neuralgia.	Mean age: 66.6 years; 208 males, 199 females.	Gabapentin ER QD (n=136) – patients took 1800 mg of gabapentin ER QD daily with their evening meal for 10 weeks. Vs. Gabapentin ER DD (n=137) – patients took 600 mg of gabapentin ER DD at breakfast and 1200 mg with evening meal daily for 10 weeks. Vs. Placebo (n=134) – patients received placebo	Baseline, weeks 2, 4, 6, 8, and 10.	The baseline observation carried forward score for gabapentin ER QD is -1.85±0.21, for gabapentin ER DD is -1.72±0.21, and for placebo is -1.42±0.21. Gabapentin ER vs. Placebo: QD p=0.110 and DD p=0.255. The last observation carried forward score for Gabapentin ER QD is -2.28±0.22, for gabapentin ER DD is -2.08±0.21, and for placebo is -1.69±0.22. Gabapentin vs. placebo: QD p=0.032 and DD p=0.154.	"The primary efficacy endpoint for this study of gabapentin ER was not met, most likely due to the unexpected large placebo response. Outcomes on secondary endpoints suggest the potential efficacy of gabapentin QD. Gabapentin ER was well tolerated in this study.	Data suggest lack of efficacy.

			provided by Michelle Héritier, PhD. RPh. formerly of Depomed, Inc. Editorial support was provided by Ed Parr. PhD. Envision Scientific Solutions, Southport, CT, USA and funded by Solvay Pharmaceuticals, Inc.			treatment for 10 weeks.				
Irving, 2009 (score=5.5)	Extended Release Gabapentin	RCT	Sponsored by Depomed Inc, Menlo Park, CA. No mention of COI.	N=158 patients with post-herpetic neuralgia.	Mean age: 70 years; 74 males, 84 females.	Gabapentin ER Once Daily (n=55) – patients received 1800 mg of gabapentin ER once daily for 5 weeks. Vs. Gabapentin ER Twice-Daily (n=52) – patients received 600 mg gabapentin AM and 1200 mg gabapentin PM daily for 5 weeks.	5 weeks.	The average daily pain score for Gabapentin ER once daily, gabapentin ER twice daily, and placebo are: change from baseline: (LS mean (95% CI)) -1.93 (-2.49, -1.37), -2.24 (-2.81, -1.67), -1.29 (-1.86, -0.71), p values for gabapentin ER vs. placebo: once daily p=0.089 and twice daily p=0.014; Percentage change from baseline: -30.1% (-38.9, -21.4), -34.7% (-43.6, -	"Gabapentin ER administered twice daily is effective and safe for the treatment of pain associated with postherpetic neuralgia."	Data suggest gabapentin ER is effective for PHN but 2-week treatment period is a relatively short treatment time.

						Vs. Placebo (n=51) – patients received the placebo daily for 5 weeks.		25.8), -18.6% (-27.6, -9.6), once daily p=0.052 and twice daily p=0.008; respectively.		
Jensen, 2009 (score=5.0)	Extended Release Gabapentin	RCT	Sponsored by Depomed Inc to the first author. Mark P. Jensen has received research support or consulting fees in the past year from Endo Pharmaceuticals and Depomed Inc, and is on the scientific advisory board of Fralex Therapeutics Inc. Yu-Kun Chiang is a consultant to Depomed Inc.	N=158 patients with post-herpetic neuralgia.	Mean age: 70 years; 72 males, 79 females.	G-ER Once Daily (n=54) – patients received a daily dose of 1800 mg of (G-ER) in the evening for 4 weeks. Vs. G-ER Twice Daily (n=48) – patients received a divided daily dose of 600mg in the morning and 1200 mg in the evening for 4 weeks. Vs. Placebo (n=49) – patients received the placebo for 4 weeks.	4 weeks.	The change between baseline and LOCF endpoint in G-ER once-daily, G-ER twice daily, and placebo for the following categories are: global pain intensity: -1.70, -2.25, -1.60, p=0.335; global pain unpleasantness: -1.76, -2.28, -1.70, p=0.423; sharp pain sensations: -1.96, -2.56, -1.39, p=0.082; hot pain sensations: -1.83, -1.39, -1.22, p=0.464; dull pain sensations: -1.77, -1.93, -0.80, p=0.051; cold pain sensations: -0.63, -0.96, -0.59, p=0.826; sensitive pain sensations -1.27, -2.37, -1.49, p=0.063; itchy pain sensations: -1.93, -2.17, -0.75, p=0.011; deep pain: -1.83, -2.28, -1.51, p=0.382;	"The results provide further support for the importance of assessing specific pain qualities as outcomes in clinical trials. The findings may also be used by clinicians for identifying those patients for whom G-ER may be particularly effective; that is, patients with postherpetic neuralgia presenting with pain described as sharp, dull, sensitive, or itchy."	Data suggests G-ER given twice per day has greater benefits on sharp, itchy, dull pain.

								and surface pain: -1.55, -1.85, -0.95, p=0.238; respectively.		
Gastroretentive Gabapentin										
Sang, 2013 (score=6.5)	Gastroretentive Gabapentin	RCT	Sponsored by Depomed Inc., Menlo Park, CA. C.N.S. has been a scientific consultant with Abbott. R.S. and M.S. are employees of and own stock in Depomed Inc.	N=452 patients with post-herpetic neuralgia.	Mean age: 65.6 years; 169 males, 293 females.	Gastroretentive Gabapentin (n=221) – patients received 300 mg/d, increased to daily dose of 1800 mg/d over 2 weeks. Patients continued stable doses of 1800 mg/d for an additional 8 weeks, followed by 1 week of dose tapering. Vs. Placebo (n=231) – patients received the placebo daily for 11 weeks.	11 weeks.	The mean change in BOCF average daily pain score from baseline to final week of treatment reports change G-GR (-2.12) compared with placebo (-1.63) (P=0.013; 95% confidence interval: -0.88, -0.11).	"Once-daily G-GR 1800mg was effective and well tolerated for the relief of pain in patients with postherpetic neuralgia."	Data suggest both groups improved with a trend towards better results with gabapentin (G-GR) in 1800 mg/d dose.
Freeman, 2015 (score=6.0)	Gastroretentive Gabapentin	RCT	Sponsored by Depomed Inc, No COI.	N=719 patients with post-herpetic neuralgia.	Mean age: 66 years; 308 males, 411 females.	G-GR (n=356) – patients received 1800 mg of Gastroretentive gabapentin once	11 weeks.	The absolute change from baseline to Week 10 in composite NPS score for placebo and G-GR are: NPS 10: -17.4 (95% CI of	"For patients with PHN, G-GR provided significant improvements in multiple measures of pain quality and	Pooled analysis from 2 phase 3 RCTs. Data suggests G-GR 1800 mg/d provides benefit to PHN patients

						daily for 11 weeks. Vs. Placebo (n=363) – patients received the placebo daily for 11 weeks.		LS mean: -19.9, -15.09), -22.2 (-24.6, -19.9), p=0.0009; NPS 8: -16.7 (-19.1, -14.3), -21.1 (-23.4, -18.8), p=0.0018; NPS NA: -17.3 (-19.8, -14.9), -22.2 (-24.5, -19.8), p=0.0008; NPS 4: -18.9 (-21.6, -16.1), -23.9 (-26.5, -21.2), p=0.0022; respectively.	pain-related functional impairment. There was a positive correlation between pain relief and improvement in patient function, with reduction in pain intensity among predictors of improvements in patients' lives. Such comprehensive analyses give an insight into numerous factors that may contribute to better management of PHN."	for pain measures.
Rauck, 2013 (score=5.5)	Gastroretentive Gabapentin	RCT	Sponsored by Depomed, Inc. Menlo Park, CA. Dr. Sweeney is a Depomed employee, owns Depomed stock, and holds Depomedstock options. Dr.Vanhove is a former	N=859 patients with post-herpetic neuralgia.	Mean age: 55.5 years; 308 males, 411 females.	G-GR (n=357) – patients received 1800 mg G-GR once daily for 10 weeks. Vs. Placebo (n=364) – patients received the placebo once daily for 10 weeks.	10 weeks.	Change in average daily pain score from baseline to week 10: G-GR -2.4, placebo -1.9, p=0.002. Percent change from baseline to week 10: G-GR -37, placebo -29, p=0.0025.	"PHN pain reduction after G-GR treatment can be observed as early as the second day of dosing and continues for at least 10 weeks."	An integrated efficacy analysis. Data suggests PHN pain may be decreased with G-GR and the benefits persist up to 10 weeks as reflected in ADP scores.

			Depomed employee. Drs. Rauck and Wallace were investigators in the Depomed studies and also serve as consultants to Depomed. Dr. Rauck is a speaker for Depomed. Dr. Irving received compensation for serving on the advisory board and the speakers bureau for Depomed. He also served on the advisory board for Eli Lilly, Endo, Neurogesx, and Zogenix.							
Gabapentin Enacarbil										
Zhang, 2013 (score=7.0)	Gabapentin Enacarbil	RCT	Sponsored by GlaxoSmithKline. Drs. Chen, Graff, and Schwartzbach, Mr. Bell, Ms. Harding, Ms. Hunter, Ms. Kavanagh, Ms.	N=371 patients with postherpetic neuralgia.	Mean age: 62.1 years; 189 males, 182 females.	GEn 1200mg (n=107) – patients took 600 mg GEn once daily in the morning for 3 days, and then twice daily thereafter. Vs.	1 week follow up.	The 24-hour average pain score change from baseline in pain intensity and sleep endpoints for GEn 1,200 mg vs. placebo is -0.81, 95% CI (-1.40, -.23), p= 0.013; for GEn 2,400 mg vs.	"The improvements in all 3 GEn treatment groups were observed as early as week 1 and maintained across all time points (Fig 2), suggesting that the advantage of GEn in comparison	Data suggest all 3 doses of gabapentin Enacarbil were beneficial for NP pain but the 1200 mg/d showed best treatment response with

			McClung, and Ms.Warren are employees of, and stakeholders in, GlaxoSmithKline. Drs. Zhang, Harden, and Freeman were Investigators in the conduct of this study and received funding from GlaxoSmithKline. Dr. Rainka was a sub-Investigator of Dr. Zhang in the conduct of this study. Drs. Harden and Freeman were paid consultants for GSK and provided input into the study design and/or interpretation of the data. Additionally, Dr. Harden has research grants from Forest, Covidien, DepoMed, DOD, and Mayday fund and has participated in			GEn 2400 mg (n=82) – patients took 600 mg GEn in the morning for 2 days, then 600 mg twice daily for 2 days, then 1,200 mg twice daily. Vs. GEn 3600 mg (n=87) – patients took 600 mg GEn in the morning for 2 days, then 600 mg twice daily for 2 days, then 1,200 mg twice daily. On day 7, subjects in the 3,600-mg group were increased to 1,800 mg twice daily. Vs. Placebo (n=95) – patients received the placebo for the 14-week treatment period.		placebo is -0.70, 95% CI (-1.33, -0.07), p=0.029; for GEn 3,600 mg vs. placebo is -1.07, 95% CI (-1.68, -0.45), p=0.002.	to existing treatments is that it provides clinically important, rapid, and durable pain relief without the necessity of a lengthy titration to an effective dosage. Doses from 1,200 to 3,600 mg divided as twice-daily dosing were efficacious although the 1,200- mg dose demonstrated the most favorable benefit:risk ratio."	least side effects.

			advisory boards with Nevro, Astrellas, Depomed, and Covidien. Dr. Laurijssens was an employee of and shareholder in GSK during the conduct of the study. Currently, he is employed by and the major shareholder in BEL Pharm Consulting, who has GSK among its clients.							
Harden, 2013 (score=5.5)	Gabapentin Enacarbil	RCT	Sponsored by GlaxoSmithKline. Drs Chen, Graff, and Schwartzbach, and Mr Bell, Ms Berges, Ms Harding, Ms Kavanagh, Ms Warren, and Ms McClung are all employees of and	N=96 patients with post herpetic neuralgia.	Mean age 63.1 years; 59 males, 37 females.	High-dose GEn (n=52) – Patients underwent baseline gabapentin treatment for 2 weeks and then received GEn (3600 mg/d) daily for 28 days, and completed a 6-day down titration period. vs.	No follow up.	Improvement in pain intensity scores with GEn 3600 vs. 1200 mg (adjusted mean [90% confidence interval] treatment difference, −0.29 [−0.48 to −0.10]; *P* = 0.013).	"While the overall results demonstrated efficacy in a PHN population, the differences between treatment periods confound the interpretation. These findings could provide insight into future trial designs."	Crossover trial. Results cannot be adequately interpreted due to differences in treatment periods.

			stakeholders in GlaxoSmithKline. Ms Hunter was an employee of GlaxoSmithKline at the time of this study. Dr Zhang was an investigator in the conduct of this study and received funding from GlaxoSmithKline. Dr Rainka was a subinvestigator of Dr Zhang in the conduct of this study. Drs Harden and Freeman were paid consultants for GlaxoSmithKline and provided input into the study design and/or interpretation of the data. Additionally,			low-dose GEn (n=44) - Patients underwent baseline gabapentin treatment for 2 weeks and then received GEn (1200 mg/d) daily for 28 days, and completed a 6-day down titration period.				

			Dr Harden has research grants from Forest, Covidien, Depomed, DOD, and Mayday Fund, and has participated in advisory boards with Nevro, Astellas, Depomed, and Covidien.							
Calkins, 2016 (score=5.5)	Gabapentin Enacarbil	RCT	Sponsored by XenoPort, Inc. AMC is on the speaker's bureaus for Pfizer, Purdue, Depomed, Teva, and Salix. JG is on the speaker's bureaus for Purdue, Salix, AstraZeneca, XenoPort, Inc., Iroko, Teva, Insys, and Depomed. BG is a speaker for UCB, Eisai, and Sunovion, and a consultant for Eisai, Sunovion,	N=371 patients with postherpetic neuralgia.	Mean age: 62.1 years; 189 males, 182 females.	GEn 1200mg (n=107) – patients took 600 mg GEn once daily in the morning for 3 days, and then twice daily thereafter. Vs. GEn 2400 mg (n=82) – patients took 600 mg GEn in the morning for 2 days, then 600 mg twice daily for 2 days, then 1,200 mg twice daily. Vs.	1 week follow up.	The mean 24-hour average pain intensity score for the last observation carried forward in the GEn 1,200mg vs Placebo is -0.81 LS mean difference, (-1.40 to-0.23) 95% CI, p=0.007; for the GEn 2,400mg vs Placebo is -0.70, (-1.33 to -0.07), p=0.029; for the GEn 3,600mg vs Placebo is -1.07, (-1.68 to -0.45), p<0.001. The Baseline observation carried forward analysis in GEn 1,200mg vs Placebo is -0.94, (-1.51 to -0.36),	"Gabapentin enacarbil (1,200 mg, 2,400 mg, and 3,600 mg) was effective and well tolerated in patients with postherpetic neuralgia compared with placebo, as confirmed by three different and robust statistical methodologies."	Data suggests GEn is effective in providing 24 hours pain relief in PHN patients at all 3 doses of 1200 mg, 2400 mg, and 3600 mg.

			Lundbeck, and Upsher-Smith. MJJ is a paid consultant of XenoPort, Inc. RK and GS are employees of and own stock in XenoPort, Inc.			GEn 3600 mg (n=87) – patients took 600 mg GEn in the morning for 2 days, then 600 mg twice daily for 2 days, then 1,200 mg twice daily. On day 7, subjects in the 3,600-mg group were increased to 1,800 mg twice daily. Vs. Placebo (n=95) – patients received the placebo for the 14-week treatment period.		p=0.001; in GEn 2,400mg vs Placebo is -0.65, (-1.27 to -0.03), p=0.040; in GEn 3,600mg vs Placebo is -0.68, (-1.28 to -0.08), p=0.027. The MMRM in GEn 1,200mg vs Placebo is -0.81, (-1.32 to -0.31), p=0.002; in GEn 2,400mg vs Placebo is -0.68, (-1.23 to -0.14), p=0.014l; in GEn 3,600mg vs Placebo is -1.07, (-1.61 to -0.54), p<0.001.		
Backonja, 2011 (score=5.0)	GabapentinEnacarbil	RCT	Sponsored by XenoPort, Inc. Dr. Backonja has received honoraria, consulting fees, or grant/research support from Endo Pharmaceuticals, GlaxoSmithKline, Johnson &	N=102 patients with postherpetic neuralgia.	Mean age: 63.3 years; 49 males, 52 females.	Placebo (n=54) – patients underwent a baseline period for a week, received open-label 600 mg gabapentin for 11 days, and then received a placebo twice daily for 2 weeks.	No follow up.	The change form baseline to end of treatment in the placebo group mean score was -1.2, in the GEN group was -2.1, p=0.0321. 30% improvement was shown in 15 placebo participants, 26 GEn participants, p=0.0073. 50% improvement was	"GEn was effective in providing PHN pain relief, improved gabapentin exposure compared with gabapentin capsules, and was generally safe and well tolerated in patients with PHN."	3 periods to study (1) baseline (2) open label (3) double-blinded RCT. Data suggest GEn better than gabapentin capsules for providing sustained

			Johnson, NeurogesX, Inc., Novartis Pharmaceuticals, Pfizer Inc., Purdue Pharma LP, Wyeth, and XenoPort, Inc. Drs. Canafax and Cundy are employees of XenoPort, Inc.			Vs. GEn (n=47) - patients underwent a baseline period for a week, received open-label 600 mg gabapentin for 11 days, and then received GEn 1,200 mg twice daily for 2 weeks.		show in 10 placebo participants, 12 GEn participants, p=0.2582.		systemic exposure.
Rauck, 2012 (4.5)	GabapentinEnacarbil	RCT	Sponsored by GlaxoSmithKline. Drs Graff, Makumi and Meno-Tetang, Ms. McClung, Ms. Kavanagh and Mr. Bell are employees of, and stakeholders in, GlaxoSmithKline. Drs. Rauck and Schwartz were Investigators in the conduct of this study and received funding from GlaxoSmithKline.	N=420 patients with diabetic peripheral neuropathy.	Mean age: 59.7 years; 249 males, 171 females.	Placebo (PBO) (n=112) – patients the placebo GEn 3 tablets twice daily or the placebo PGB 1 tablet 3 times daily for 20 weeks. Vs. GEn 1,200 mg/day (n=56) – patients received GEn 600 mg tablet twice daily ot the PGB placebo 1 tablet, 3 times daily for 20 weeks.	1 week follow up.	Treatment difference vs placebo for change from baseline in mean 24 hour average pain intensity score at end of maintenance treatment in GEn 1,200 mg is -0.35, (-1.02, 0.31) 95% CI, p=0.295; in GEn 2,400 mg is -0.02, (-0.71, 0.66), p=0.946; in GEn 3,600 mg is -0.55, (-1.10, 0.01), p=0.105; in PBG is 0.43, (-0.22, 1.08), p=N/A.	"Overall, none of the GEn treatment groups differentiated from placebo. Analyses of the secondary endpoints showed comparable results across treatment groups. However, the majority of the endpoints, including all of the pain endpoints, showed the largest numerical treatment difference was between GEn 3,600 mg and placebo. The active control, PGB (300 mg/day), did not	Unequal randomization. All treatment groups showed efficacy except PGB (pregabalin) and placebo group.

			Dr. Rauck was a paid consultant for GSK and also involved in the interpretation of the data.Declarations of Interest: Drs Graff, Makumi and Meno-Tetang, Ms. McClung, Ms. Kavanagh, Mr. Bell are employees of GlaxoSmithKline and have no other conflicts of interest to declare. Dr. Rauck and Dr. Schwartz have no other conflicts of interest to declare.			Vs. GEn 2,400 mg/day (n=56) – patients received either GEn 600 mg, taken 2 tablets twice daily, or the PGB placebo, taken 1 capsule 3 times a day for 20 weeks. Vs. GEn 3,600 mg/day (n=112) – patients received 600 mg GEn 3 tablets twice daily or PGB placebo taken 1 capsule 3 times daily for 20 weeks. Vs. PGB 300 mg/day (n=56) – patients received either 100 mg PGB taken 1 capsule 3 times daily or GEn placebo taken 3 tablets			differentiate from placebo."	

						twice daily for 20 weeks.				

Pregabalin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Lesser 2004 (score = 9.5)	Pregabalin	RCT	Sponsored by Pfizer Global Research and Development. No mention of COI.	N = 337 with painful diabetic neuropathy	Mean age is 59.9 years. 202 males, 135 females.	Placebo (n = 97) vs. pregabalin 75mg a day (n = 77) vs. 300mg (n = 81) vs. 600mg a day (n = 82). Dose was titrated for 1 week for 600mg group and all had 4 weeks of fixed dosing.	Follow up 1 week after 5 week treatment.	At least 50% pain reduction in 18% of placebo group, 46% at 300mg and 48% at 600mg. The 75mg group not significantly different than placebo.	"In patients with diabetic peripheral neuropathy, pregabalin demonstrated early and sustained improvement in pain and a beneficial effect on sleep, which were confirmed by positive patient global impression. Pregabalin was well tolerated at all doses."	Adverse events included dizziness, somnolence, peripheral edema, blurry vision, confusion, and accidental injury. Some efficacy suggested.
Dworkin 2003 (score = 9.0)	Pregabalin	RCT	Supported by Pfizer Global Research and Development, Ann Arbor, MI. R.H.D. received a research grant from Pfizer for participating in the clinical trial described in this article but was not compensated for article	N = 173 with postherpetic neuralgia	Mean age is 71.5 years. 92 males, 81 females.	Pregabalin (n = 89): dose titrated from 50mg TID the first 3 days, then 100 TID for 4 days, then 200mg TID following week for those with creatinine clearance (>60mL/min) vs.	Follow up at weeks 1,3,5, and 8.	Pain scores significantly improved by Day 2. More had at least 30% pain reduction in pregabalin group (63% vs. 25%); 50% vs. 20% had at least 50% pain reduction. Marked differences in McGill scores (9.85 vs. 14.72). Endpoint mean pain scores (pregabalin	"Treatment of PHN with pregabalin is safe, efficacious in relieving pain and sleep interference, and associated with greater global improvement than treatment with placebo."	Dropout rate elevated in pregabalin. Adverse effects primarily related to CNS and included dizziness, somnolence, amblyopia, dry mouth, abnormal gait, ataxia, confusion, speech disorder, and peripheral edema.

			preparation; he has received research grants, consulting fees, or speakers' bureau honoraria in the past year from Akros Pharma, AstraZeneca, Elan Pharmaceuticals, Endo Pharmaceuticals, GlaxoSmithKline, King Pharmaceuticals, NeurogesX, Novartis, Ortho-McNeil Pharmaceutical, Pfizer, Reliant Pharmaceuticals, and UCB Pharma; consulting fees and speakers' bureau honoraria in excess of $10,000 were received from Novartis and Pfizer.			placebo (n = 84) for 8 weeks.		vs. placebo): 3.60±0.24 vs.5.29±0.23, p = 0.0001.		
Richter 2004 (score = 9.0)	Pregabalin	RCT	Supported by Pfizer Global Research and Development,	N = 246 with painful diabetic neuropathy	Mean age is 57.1 years. 149	Placebo (n = 85) vs. pregabalin 150mg a day (n = 79) vs. 600mg a	Follow up at 6 weeks.	Less sleep interference on pregabalin especially at 600mg	Study "demonstrates that pregabalin…is an efficacious and	Adverse events were dizziness, somnolence, peripheral edema,

			Ann Arbor, Michigan. No mention of COI.		males, 97 females.	day (n = 82) for 6 weeks.		a day. At trial end, complete relief of allodynia 22.7% of placebo compared to 56.5% at 150mg a day vs. 64.3% at 600mg a day.	safe treatment for the pain of this condition."	headache, asthenia, weight gain, amblyopia.
Stacey 2008 (6.5)	Pregabalin	RCT	Sponsored by Pfizer Inc. No mention of COI.	N = 269 patients with PHN.	Mean age is 67.4 years. 150 males, 119 females.	Placebo (N=90) vs. Pregabalin; Flexible dose (N=91) vs. Fixed Dose (N=88).	Follow up at weeks 1 and 4.	Flexibly adjusting the dose of pregabalin up to a maximum of 600 mg/day by week 2 enhances efficacy and tolerability. In the fixed dose group, 19% of patients discontinued treatment due to adverse effects. Median time to pain relief was not significantly significant.	"Pregabalin fixed- and flexible-dose regimens produce significant and measurable reductions in pain as early as 1.5 days and 3.5 days, respectively, in patients with PHN, and reductions in allodynia after 1 week."	Data suggest utilization of flexible pregabalin dosing may result in slightly higher pain relief. Flexible dosing should be patient specific based on benefit and tolerability.
Holbech 2015 (6.5)	Pregabalin	RCT	Sponsored by Pfizer with a grant of USD 52080 (grant no:WS368802). Also supported by a grant from Odense University Hospital. One or more authors have a COI.	N = 73 patients with painful polyneuropathy.	Mean age is 59.1 years.	mITT (N=69) vs. PP (N=48)	Follow up at 5 weeks.	The fifth week of treatment between placebo and the 3 active treatments were: combination = -1.67 (-2.11 to -1.23), imipramine = -1.08 (-1.52 to -0.64), and pregabalin = -0.48 (-0.92 to -0.04). Combination treatment had significantly lower pain score the	"Combination of moderate doses of the tricyclic antidepressant imipramine and pregabalin could be considered as an alternative to high-dosage monotherapy."	Data suggest combination therapy resulted in lower pain scored but this had higher reported side effects.

								pregabalin (P<0.001) and imipramine (P=0.009).		
Cardenas 2013 (6.0)	Pregabalin	RCT	Funded by Pfizer Inc. One or more authors have a COI.	N = 220 patients with chronic, below-level neuropathic pain due to spinal cord injury.	Mean age is 45.9 years. 176 males, 43 females.	Placebo (N=108) vs. Pregabalin (N=111).	Follow up at 12 and 16 weeks.	97 placebo patients and 100 pregabalin patients had adequate sleep (p=0.100). 97 placebo and 100 pregabalin had snoring (p=0.105). 98 placebo and 100 pregabalin awoke with shortness of breath (p=0.035). 98 placebo and 100 pregabalin had a sleep quantinty (p=0.044). 97 placebo and 100 pregabalin had somnolence (p=0.276).	"This study demonstrates that pregabalin is effective and well tolerated in patients with neuropathic pain due to SCI."	Data suggest pregabalin at doses ranging from 150 mg/day to 650 mg/day has efficacy for decreasing spinal cord related NP.
Smith, 2013 (score=6.0)	Pregabalin vs Placebo vs Carisbamate	RCT	Sponsored by Janssen Research & Development, LLC, Raritan, N.J., U.S.A. Dr. Smith's employer received compensation from Janssen Research & Development	N=386 patients with painful diabetic neuropathy or post-herpetic neuralgia.	Mean age: 58±8.94 years; 225 males, 161 females	Study 1&2: Patients received carisbamate 400 mg/day or placebo for 4 weeks vs Study 3: received either 800 mg/day, 1200 mg/day, pregabalin 300 mg/day, or placebo for 15 weeks	8 weeks, 15 weeks	Square mean differences between carisbamate and placebo groups were study 1: -0.512 carisbamate 400 mg/day; study 2: -0.307 carisbamate 400 mg/day; and study 3: -0.51 carisbamate 800 mg/day; -0.55 carisbamate 1200 mg/day; and -0.43	"Carisbamate, although well tolerated, did not demonstrate efficacy in neuropathic pain across these studies, nor did the active comparator pregabalin"	Pooled analysis from 3 RCTs. Data suggest comparable in efficacy between all groups.

			for study conduction.					pregabalin 300 mg/day. Neither caribamate nor pregabalin differed from placebo for all 3 studies.		
Barbarisi 2010 (5.0)	Pregabalin	RCT	No mention of sponsorship or COI.	N = 30 patients with neuropathic pain.	Mean age is 64.5 years. 15 males, 15 females.	P300+TENS (N=9) vs. P300 TENS-placebo (N=8) vs. P600-TENS (N=7) vs. P600+TENS-placebo (N=6)	Follow up at 4 weeks.	P300+TENS had a reduction of pain of 40%. TENS + Placebo group had changes of 10% and 16%. P300+TENS vs P300+TENS showed statistically significant reduction of VAS (25 vs 39). P600+TENS vs P600+TENS placebo also showed statistically significant reduction in VAS score (23 vs 32).	"The use of Pregabalin with TENS resulted in a significantly better reduction of pain and sleep interference in all selected patients."	Small sample. Data suggest the combination of pregabalin and TENS better than pregabalin alone for PHN pain and less sleep dysfunction.
Tölle 2008 (5.0)	Pregabalin	RCT	Funded by Pfizer Inc. Drs Tolle and Freynhagen have received research support and have been reimbursed for travel related expenses to clinical meetings.	N =395 patients with painful diabetic neuropathy.	Mean age is 85.75 years. 219 males, 176 females.	Placebo (N=93) vs. Pregabalin 150 mg/day (N=96) vs. Pregabalin 300 mg/day (N=96) vs. Pregabalin 600 mg/day (N=98).	Follow up at 12 weeks.	Endpoint mean scores for placebo 150, 300, and 600 mg/day pregabalin were: 4.5 (-1.9) 4.1 (-2.1), 4.4 (-2.1) and 3.7 (-3.0) respectively. The 600 mg/day pregablin group was significantly superior to placebo ($p<0.01$).	"Pregabalin 600 mg/day (administered in two divided doses) was well tolerated by these patients with painful DPN and was significantly superior to placebo in reducing pain and pain-related sleep interference and in improving overall patient health	Data suggest a statistically significant reduction in pain for the 600 mg pregabalin group but this group also reported more adverse events.

									status and quality of life".	
Sabatowski 2004 (5.0)	Pregabalin	RCT	Sponsored by Parke-Davis which merged with Pfizer during study. One or more authors have a COI.	N = 238 patients with neuropathic pain of PHN.	Mean age is 72.1 years. 107 males, 131 females.	Placebo (N=81) vs. Pregabalin 150 mg/day (N=81) vs. Pregabalin 300 mg/day (N=76)	8 week follow up.	The ITT population had a statistical significant of responding patients (decreased pain score of at least 50%) (26%, p=0.006) as well as the 300 mg/day pregablalin group (28%, p=0.006) compared to the placebo group (10%).	"Pregabalin efficaciously treated the neuropathic pain of PHN. Additionally, pregabalin was associated with decreased sleep interference and significant improvements in HRQoL measures."	Data suggest pregabalin administered either 50 mg 3 times per day or 100 mg 3 times per day effectively treated PHN associated pain with the higher dose showing more benefit than the lower dose.
van Seventer 2006 (5.0)	Pregabalin	RCT	Funded by Pfizer. One or more authors have a COI.	N = 368 patients with neuropathic pain.	Mean age is 70.7 years. 168 males, 200 females.	Placebo (N=93) vs. Pregabalin 150 mg/day (N=87) vs. Pregabalin 300 mg/day (N=98) vs. Pregabalin (N=88).	Follow up at 13 weeks.	Endpoint mean score was significantly improved for each pregabalin dosage group compared with placebo. All three pregabalin groups demonstrated significantly superior improvements in weekly mean pain score beginning at Week 1 (p=0.0005 for 150mg/day); (p=0.0002 for 300 and 600 mg/day).	"Pregabalin, dosed BID, reduced neuropathic pain associated with PHN and was well tolerated. It also reduced the extent to which pain interfered with sleep."	Study consisted of 3 phases. Data suggest pregabalin dosed twice per day provides NP pain relief and helps with sleep abnormalities.
Haanpää, 2015 (score=5.0)	Pregabalin vs	RCT	Sponsored by Astellas Pharma Europe Ltd. COI:	N=568 patients with peripheral	Mean age: 55.0 years; 245 males,	Capsaicin group (n=282):	4 weeks	Patients achieving a ≥30% decrease in mean NRPS score	"The capsaicin 8% patch provided non-inferior pain	Open label non-inferiority trial, data suggest capsaicin 8%

	Capsaicin patch		Professor Maija Haanp€a€a was principal investigator for the ELEVATE study. She has received honoraria from Astellas for speaking at sponsored meetings. Dr William McBride as a member of the independent data review board received a fee for service from Astellas. He was a speaker at an Astellas sponsored symposium on 7th October 2014 at IASP. Professor Giorgio Cruccu received a fee for service from Astellas as	neuropathic pain	314 females	received 640 lg/cm2 [8% weight for weight]) capsaicin patch vs Pregabalin group (n=277): received oral pregabalin		was 55.75 for capsaicin group and 54.5% for pregabalin group. Mean pain relief time was short for capsaicin group compared to pregabalin group, 7.5 days vs 36 days respectively (p<0.0001).	relief to an optimized dose of pregabalin in PNP, with a faster onset of action, fewer systemic side effects and greater treatment satisfaction."	patch performed quicker for pain relief than the oral pregabalin (7.5 days vs 36 days).

			member of the Independent Review Board for the ELEVATE study. He has worked with Astellas, Convergence, Lilly and Pfizer. Professor Turo Nurmikko has received fees for service from Astellas for speaking and acting as Chairman of the Independent Review Board for the ELEVATE study. Dr Bosilkov received financial remuneration from Astellas Pharma for participation in the ELEVATE							

			study based on the study contract conditions. E Ernault, C Chambers, and A Abdulahad are employed by Astellas Pharma Europe.							
Freynhagen 2005 (4.5)	Pregabalin	RCT	Funded by Pfizer. On or more authors have a COI.	N = 338 with chronic postherpetic neuralgia (PHN) or painful diabetic peripheral neuropathy (DPN).	Mean age is 62.2 years. 183 males, 155 females.	Placebo (N=65) vs. Pregabalin Flexible-dose (N=141) vs. Pregabalin Fixed-dose (N=132)	Follow up at 12 weeks.	Treatment with either pregabalin regimen resulted in statistically significant improvement in pain symptoms compared with placebo. 48.2% of patients treated with flexible dose pregablain, 52.3% of patients treated with fixed-dose pregabalin, and 24.2% of patients on placebo experienced a >50% pain score reduction (P<0.001 for each pregabalin group compared to placebo).	"Flexible BID dosing of pregabalin, allowing for dosage adjustment to optimize tolerability and efficacy, is recommended."	High dropout rate. Data suggest efficacy of pregabalin for improvement of neuropathic pain but dosing should consider a balance of benefits versus risks (adverse events) such as periperhal edema.

van Seventer 2010 (4.5)	Pregabalin	RCT	Funded by Pfizer Inc. No mention of COI.	N = 367 patients with post-traumatic peripheral neuropathic pain.	Mean age is 51.5 years. 125 males, 129 females.	Placebo (N=127) vs. Pregabalin (N=127)	Follow up at 8 weeks.	The percentage of patients with >30% pain reduction in pain from baseline to end-point was significantly greater in the pregabalin group (39.7%) than in the placebo group (25.4%; P<0.05). Statistical significance in favor for pregabalin was apparent at week 3 (P=0.01) and then weekly from week 5 to week 8 (P<0.05).	"Flexible-dose pregabalin 150–600 mg/day was effective in relieving neuropathic pain, improving disturbed sleep, improving overall patient status, and was generally well tolerated in patients with post-traumatic peripheral neuropathic pain."	Data suggest most (approximately 2/3) patients considered themselves improved with pregabalin both in terms of pain and sleep as well as depression.
Karmakar 2014 (4.5)	Pregabalin	RCT	Funded through receipt of a Neuropathic Pain Research Award in 2009 from Pfizer Canada. One or more authors have a COI.	N = 19 patients with at least moderate diabetic peripheral neuropathic pain..	Mean age is 65.7 years. 16 males, 3 females.	Placebo (N=19) vs. Pregabalin (N=19).	1 week follow up period.	No significant differences in duration of time to walk 50 meters. No significant differences for high and low contrast visual acuity, proprioceptive thresholds.	"Analgesia did not decrease gait variability in PDPN patients, and in fact, increased gait variability was seen during pregabalin treatment."	Data suggest DM patient with NP pain receiving analgesia had increased gain variability.
Škvarč 2010 (4.0)	Pregabalin	RCT	No mention of sponsorship. No COI.	N = 29 patients who had herpes zoster pain.	Mean age is 65 years. 10 males, 19 females.	Placebo (N=15) vs. Pregabalin (N=14)	Follow up at 3 weeks.	Mean duration of pain was 12 days for pregablin and 11 days for placebo. No significant differences between the groups in manifestation of SHN or PHN. The most common	"This study did not prove that pregabalin had any statistically signifi cant additional impact on pain relief in patients with acute zoster pain, or in the appearance of SHN	Data suggest lack of efficacy but increased incidence of adverse effects.

								adverse affect was dry mouth (65.6%). 55.2% patients were tired, 44.8% were dizzy, 44.8% somnolence, 41.4% vertigo, 20.7% constipation, 17.2% diplopia, 13.8% flatulence. Patients in the pregabalin group had more adverse effects than placebo group (52 vs. 36).	or PHN, in comparison with patients treated with a placebo."	
Liang 2015 (4.0)	Pregabalin	RCT	No mention of sponsorship. No COI.	N = 300 patients suffering from herpes zoster with moderate to severe neuropathic pain.	Mean age is 65.0 years. 133 males, 167 females.	Group A received oral controlled-released (CR) oxycodone (N=150) vs. Group B who received oral pregabalin in addition to CR oxycodone (N=150)	Follow up at 4 weeks.	All four groups had significant NRS decrement compared with baseline . Quality of life increased in all groups and pregabalin –treated patients had the most improvement (BPI score of 72.7% for group B vs 63.7% in group A $p<0.05$). Tolerated dose of oxycodone was lower while pregabalin had acceptable tolerability.	"Pregabalin, combined with oxycodone, was associated with significantly decreased pain intensity and improved quality of life with acceptable tolerability."	Data suggest combination morphine and pregabalin had similar results as morphine monotherapy which would suggest each of efficacy for pregabalin.
Bouhassira, 2014 (score=4.0)	Pregabalin	Post Hoc RCT	Sponsored by Eli Lilly & Company. More than one of the authors have received or will	N = 790 patients with diabetic peripheral	Mean age: 61.6 years; 442 males, 348 females.	In the initial therapy period of 8 weeks, Cluster 1a, 2a, 3a of 60mg of	Follow-up at baseline, 4, 8, 12, and 16 weeks.	Three clusters were formed based on similar Neuropathic Pain Symptom Inventory (NPSI)	"The present exploratory analyses further support the hypothesis that	Data suggest 3 different pain profile groups via NPSI phenotyping witch may assist in

			receive benefits for personal or professional use from Eli Lilly & Company.	neuropathic pain (DPNP).		duloxetine/day groups (N=112, N=154, N=132 respectively), vs Cluster 1b, 2b, 3b 300mg of Pregabalin/day groups (N=120, N=126, N=146). In the 2nd therapy period of 8 weeks, cluster 1a, 2a, 3a combination therapy of 60 mg duloxetine and 300 mg pregabalin/day (N=50, N=68, M=48), vs cluster 2a, 2b, 2c monotherapy of 120mg duloxetine or 600 mg of pregabalin (N=54, N=62, N=52).		responses. In the initial 8 week therapy period, significant results were seen in reduced Brief Pain Inventory (BPI) scores in cluster 2 and 3 for duloxetine (p=0.020, p=0.002 respectively). In the 2nd 8 week therapy period, there were no statistically significant difference between clusters 1 2 or 3 (p=0.090, p=0.107, p=0.310 respectively).	variability in sensory profiles exists across patients with diabetic peripheral neuropathic pain. In essence, the identification of subgroups of patients with distinct pain characteristics at baseline and their differential responses to duloxetine and pregabalin, alone or in combination, is encouraging, and indicates that heterogeneity in the patient population should be taken into account for a more stratified or even personalized treatment approach."	individualized treatment plans regarding the dosing of both duloxetine and pregabalin.

Mirogabalin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Vinik 2014 (4.5)	Mirogabalin	RCT	Supported by Daiichi Sankyo. On or more authors have COI.	N = 452 patients with diabetic	Mean age is 60.1 years. 242 males,	Placebo (N=112) vs. Pregabaline (N=56) vs. Microgabalin; 10	Follow up at 5 weeks.	LS mean difference in ADPS from baseline to 5 weeks were -0.22, -0.53, -	"Mirogabalin 15, 20, and 30 mg/day had statistically significant	Data suggest mirogabalin at doses of either 15, 20, or

				neuropathic pain	210 females.	(N=57), 15 (N=57), 20 (N=56), 30mg/day (N=57).		0.94, -0.88, and -1.01 for placebo; 5-, 10-, 15-, 20-, and 30- for mirogabalin; and -0.05 for pregabalin. Placebo versus mirogabalin results were statistically significant (P<0.05). Pregabalin vs placebo at weeks 1 and 2 were statsically significant but not at weeks 3, 4, and 5.	reductions in ADPS versus placebo, and mirogabalin 30 mg/day also met the criteria of minimally meaningful effect."	30mg/day had statistically significant ADPS reductions versus both placebo and pregabalin and was generally well tolerated.
Hutmacher 2016 (4.5)	Mirogabalin	RCT	No mention of sponsorship. One or more authors have COI.	N = 436 patients with DPNP.	Mean age is 61 years. 231 males, 205 females.	Placebo (N=109) vs. Mirogabalin (N=272): 5, 10, 15, 20, 30 mg/day vs. 300 mg/day Pregabalin (N=55)	Follow up at 5 weeks.	The effect of pregabalin seemed to wane as time went on (week 2 and after). Mirogabalin was estimated to be17-fold more potent than pregabalin. The effectiveness of 150 mg pregabalin, dosed twice daily, attenuated by week 5.	"Twice-daily dosing of mirogabalin was predicted to yield a lower incidence rate of dizziness than once-daily dosing; thus, titration of dosages should reduce adverse event rates."	Data suggested twice per day dosing of mirogabalin will decrease both dizziness and somnolence based on the exposure-response model.

Antivirals

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Tyring, 2000 (score=6.5)	Antivirals	RCT	No mention of COI or sponsorship.	N=597 patients with herpes zoster	Age group: >50 years;	Valacyclovir group (n=297): received 1 gram	24 weeks	More patients showed prodromal pain for valacyclovir	"This double-blind, randomized comparison of	Data suggest comparable efficacy for pain

	Valacyclovir, Famciclovir				no mention of sex.	3 times daily for 7 days vs Famciclovir group (n=300): received 500 mg 3 times daily for 7 days		group compared to famciclovir group (78% vs 70%, p=.03) with higher severity as well (34% vs 24%, p=.03).	valacyclovir and high-dose famciclovir in acute herpes zoster did not detect differences between treatments on the main clinical outcome measure of zoster-associated pain, rash healing, and postherpetic neuralgia."	relief asscociated with HZ.
McKendrick, 1986 (score=4.5)	Antivirals Acyclovir vs Placebo	RCT	No mention of sponsorship or COI.	N = 205 elderly patients with herpes zoster.	Mean age of acyclovir group: 72.9, Placebo group: 70.8 Sex(M:F) 87:118	The treatment group (N = 100) received 800 mg acyclovir five times per day, for 7 days. The placebo group (N = 105) followed the same protocol as the treatment group with administration of 800 mg placebo.	5 months or until cessation of pain.	Acyclovir showed significant reductions in the time to arrest of new lesion formation (p=0.005), loss of vesicles (p<0.001), and full crusting (p=0.02) when compared to the placebo group. A significant decrease in pain during treatment was seen in the acyclovir group vs. the placebo group (p=0.008)	Oral acyclovir may modify acute herpes zoster and reduce pain in afflicted patients. The benefits may be more substantial if treatment is given within 48 hours of the onset of the rash.	Data suggest oral acyclovir may reduce pain associated with HZ as well as modify the duration and acuity.

McKendrick, 1989 (score=4.0)		RCT	No mention of sponsorship or COI.	N = 376 elderly patients with herpes zoster.	Mean age of Acyclovir group: NA Placebo group: NA Sex(M:F) NA	The treatment group (N = 181) received 800 mg acyclovir five times per day, for 7 days. The placebo group (N = 183) followed the same protocol as the treatment group with administration of 800 mg placebo.	6 months or until cessation of pain.	At 1-month follow-up 61% of patients still had some pain. At 3-month and 6-month follow-up 24% and 13% had pain, respectively.	The data shows no evidence supporting the claim that acyclovir has an effect on the incidence or severity of postherpetic neuralgia.	Data suggest lack of efficacy for long term benefit of pain relief.
Mckendrick, 2009 (score = 4.0)										9 year follow up to McKendrick 1986. Data suggest no association at 9 years between pain nor absence of pain and use of acyclovir at the time of discharge in the original study, which suggests no clean benefit from the use of acyclovir.

Homeopathy and/or Complimentary Medicine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Motilal, 2013 (score=7.0)	Complimentary Medicine Topical Nutmeg	RCT	No mention of sponsorship. No COI.	N = 74 patients with diabetes and painful neuropathy.	Mean age: 60.2 years; 24 males, 50 females.	All groups 4 sprays of assigned treatment to affected area 3 times a day for 4 weeks. Topical nutmeg extracts (NEMM)mace oil 2%, nutmeg oil 14%, methyl salicylate 6%, menthol 6%, and coconut oil) (N = 37) Vs MM placebo (MM) methyl salicylate 6%, menthol 6%, coconut oil, and alcohol) (N = 37)	4 weeks	Brief Pain Inventory for Diabetic Painful Neuropathy (BPI-DPN) NEMM vs MM worst pain 4.65 vs 4.35 (p = 0.594) average pain 4.43 vs 4.41 (p = 0.970) walking ability 1.05 vs 1.19 (P = 0.9430 Sleep 1 vs 1.11 (p = 0.694) Neuropathic Pain Symptom Inventory (NPSI) Total NPSI 15.67 vs 15.32 (p = 0.620)	"In this trial topical, nutmeg extracts did not add to the improvements observed in PDN symptoms during 4 weeks treatment with preparations containing menthol and methyl salicylate. Further research designed to test the individual components of the topical therapies used in this study may clarify their benefit."	Data suggest each of efficacy.
Sindrup 2000 (5.5)	Complimentary Medicine St. John's wort	RCT	Sponsorship by a grant from the Foundation of 1870 and the Danish national Research council.	N = 54 patients with polyneuropathy and pain of more than 6 months	Mean age: 58 years; 31 males, 16 females.	St john's wort (n=27) - 900 micrograms of totalhypericin 3 tablets a day for 5 weeks.	5 weeks, 10 weeks.	Pain symptoms St. John's wort vs Placebo 14 vs 15 (p = 0.05) pain processing heat pain threshold 50.1 vs 50.8 (p = 0.12) pressure pain threshold	"This study found no significant effect of St. John's wort on painful polyneuropathy. Measures of pain processing were	Data suggests minimal trend of decreased pain with St. John's wort but no significant effect.

			No mention of COI.			vs Placebo (N = 27) - Cross over after 1 week washout.		165 vs 183 (p = 0.07). Pain relief Complete or good 6 vs 0 moderate 3 vs 2 slight 4 vs 7 None 22 vs 25 worse 12 vs 13 (p = 0.07) Side-effects none 34 vs 32 light 8 vs 7 bothering 4 vs 6 unacceptable 1 vs 2 (p = 0.58)	also unaltered by St. John's wort."	
Hui 2012 (5.0)	Complimentary Medicine CAM Intervention	RCT	Sponsored by St. Michael's Hospital Department of Family and Consumer Medicine. No COI.	N = 59 patients with Herpes Zoster and moderate posttherapuitic neuralgia pain.	Mean age: 69.75 years; 24 males, 35 females.	Immediate treatment group (IMG) (n=32) – received the CAM intervention once daily, five days per week, for three weeks. Wait-list group (WLG) (n=27) – received the same treatment and the IMG group starting three weeks after randomization.	Baseline, 3 weeks, 6 weeks, 9 weeks.	At baseline the Likert Pain Scale Scores were 0% for IMG and WLG. At 3 weeks the LPS scores were -70% for IMG and -4% for WLG, p<0.001. At 6 weeks the LPS scores were -52% for IMG and -36% for WLG. At 9 weeks the LPS scores were -52% for IMG and -32% for WLG.	"The described CAM protocol was associated with significantly reduced sub-acute and chronic post-herpes zoster neuralgia pain with three weeks if initiating treatment. Improvements persisted for up to two years"	Waitlist control and contact biases. Data suggests CAM may be effective for decreasing chronic HZ associated pain up to 9 weeks but trial of neural therapy, cupping and bleeding, meditation and Chinese herbs.
Li 2010	Complimentary Medicine	RCT	Sponsored by Origin Biomed	N = 60 patients with	Mean age: 69 ± 10	Neuragen PN (n=30) – patients	Every hour till hour 9.	The Mean VAS pain results for Neuragen PN	"This randomized, placebo controlled,	Crossover design. Sparse

(4.5)	Neuragen PN		Inc, Reilly Family Foundation, and Louisiana Life Course and Aging Center. No mention of conflict of interest.	physician diagnosed peripheral neuropathy.	years; 24 males, 36 females.	applied the Neuragen PN, which consisted of homeopathic and plant extract ingredients, to the skin of the participant's feet. Placebo (n=30) – patients applied the placebo, which consisted of USP light mineral oil with 5% v/v cis rose oxide, to the skin on their foot.		and the placebo Pre and Post application were 4.7 and 2.53 for the Neuragen PN group and 4.2 and 3.98 for the placebo group. Neuragen PN had significantly great pain reduction effects than the placebo ($p<0.05$). 52% of patients in the Neuragen PN group received maximal pain relief of >50% within 30 minutes of application compared to the 3% in the placebo group.	clinical trial with crossover design revealed that the naturally derived oil, Neuragen PN®, provided significant relief from neuropathic pain in an all cause neuropathy group. Participants with diabetes within this group experienced similar pain relief."	methods. Data suggests Neuragen PN provided significant relief for 8 hours compared to placebo.

Acupuncture

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Lewith 1983 (6.5)	Acupuncture	RCT	Sponsored by grant from Wessex Regional Health Authority. No mention of COI.	N=62 patients with post-herpetic neuralgia	Mean age: 72.1 years; 20 males, 42 females.	Acupuncture group (n=30) vs Placebo group (n=32)	Weekly for 8 weeks.	Two-point change in pain score was observed in acupuncture group and the mock TNS group. ($x^2 = 0.02$, df= 1, ***P*** **=**0.9).	"This suggests that acupuncture is of little value as an analgesic therapy for post-herpetic neuralgia, However the study method and the use of a mock tramcutaneous nerve stimulator as a placebo may be of value when assessing the effects of acupuncture in other conditions."	Data suggest (in)efficacy.

Garrow 2014 (6.0)	Acupuncture	RCT	No COI and sponsored by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (grant reference number PBPG-0706-10595).	N=45 patients with diabetic painful neuropathy (DPN)	Mean age: 65.67 years; 31 males, 14 females	Acupuncture group (n=24): received acupuncture with needles in place for 30 min and manipulated after 15 minutes with ten weekly sessions vs Sham control (n=21: received same session style with sham needles that don't penetrate skin	10 weeks	Acupuncture group show a 16% improvement in LANSS score. Sham group showed 7.2% deterioration in LANSS symptoms. Six of 24 acupuncture patients showed 25% improvement compared to sham with only 19%. LANSS score improved by average of 2.1 points more in treatment group than sham group. Acupuncture group also showed improvement in VAS pain intensity, MYMOP scores, SPS, and DBP, and SF-36. Sham group also showed improvements in these groups, but were much smaller.	"We have demonstrated the practicality and feasibility of acupuncture as an additional treatment for people with DPN. The treatment was well tolerated with no appreciable side effects. Larger randomised trials are needed to confirm the clinical and cost-effectiveness of acupuncture in the treatment of DPN."	Pilot RCT. Data suggests a trend towards improvement in DPN associated pain.
Ursini 2011 (3.0)	Acupuncture	RCT								Nested, open label study, High dropout rate. Many of the randomiz

										ed patients did not receive the allocated interventi on.
Pan 2008 (1.5)	Acupuncture	RCT								Sparse methods. Little data regarding group characteri stics.

Electroacupuncture

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Penza 2011 (4.5)	Electroacup uncture	RCT	Sponsored by a grant (No. 302/14616/ 2005) to GL from the Family and Social Solidarity Council of the Regione Lombardia, Italy. No mention of COI.	N=16 patients with axonal polyneuropat hy	Mean age: 64.9 years; 7 males, 9 females	EA (n=8) - received electroacupunct ure for six sessions 30 minutes each at interval of 5-7 days. Psuedo-EA (n=8) - placebo received with needle in neutral anatomical points with electrical stimulations.	12 weeks	EA group showed pain intensity at baseline of 5.7±2.3 and 4.97±3.23 after treatment. Pseudo-EA group was 4.9±1.9 at baseline and 4.18±2.69 after treatment. Only 1 patient in each groups reported 50% of pain relief after treatment.	"Our results do not support the use of EA in this population of painful neuropathy patients. Further studies in larger groups of patients are warranted to confirm our observation."	Crossover design. Small sample. Data suggests (in)efficacy.

Peripheral Nerve Adjustment

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ke 2013 (6.5)	Peripheral Nerve Adjustment	RCT	Sponsored by Shanghai Jiao Tong University scientific research funding, Shanghai Education Committee scientific research funding [No 11YZ56] and Science and Technology Commission of Shanghai Municipal [No 12ZR1419900]. No mention of COI.	N = 102 patients with Postherpetic Neuralgia (PHN) resulting from Herpes Zoster.	Mean age: 70.2 years; 58 males, 44 females.	Group A (n=34) – Blank control. Received disinfectant onto the affected skin region without further peripheral nerve adjustment. Group B (n=34) – Treatment with peripheral nerve adjustment. Received peripheral nerve adjustment under the region of sin affected by PHN. Group C – (n=34) Positive control group. Following routine of skin disinfection, a cannular need was inserted under the skin, but no nerve adjustment was made.	Day 1, 3, 7, 14, and 38 following treatment.	At day 1 the difference between the VAS scores of groups A and B = 1.33 ± 0.25, $P < 0.0001$; between B and C = 1.39 ± 0.26, $P < 0.0001$. Significant interaction between treatment group and follow-up time ($p<0.001$).	"We conclude that peripheral nerve adjustment can relieve PHN pain and improve patients' quality of life. The possible mechanisms involved may include the reduction of both peripheral and central sensitization, the modulation of nerve plasticity, and an increase in endogenous analgesic molecules."	Experimental group, Sham group, and Placebo group. Data suggest experimental group experienced improvement of quality of life and decreased pain vs other two groups.

Anti-inflammatory Agents - P-38 MAP Kinase Inhibitors

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Anand, 2011 (score=5.5)	Anti-inflammatories Dilmapimod	RCT	Sponsored by GlaxoSmithKline and COI: authors Joanne E. Palmer, Amanda J. Baines, Robert Y.K. Lai, Jonathan Robertson, Nick Bird, Thor Ostenfeld and Boris A. Chizh were GSK employees at the time of the study. Imperial College London received financial support from GlaxoSmithKline to fund the investigation and Dr. Ravikiran Shenoy in his capacity as clinical trial investigator.	N=40 patients with peripheral neuropathic pain	Mean age: 55.1 years; 26 males, 24 females	Oral dilmapimod: received 7.5 mg BID for 14 days vs Placebo	1, 7, 14 days	Mean difference between PI-NRS reduction was 0.67 [95% CI (0.24, 1.09); p = 0.0027]. Reduction in daily CPI of 0.64 [95% CI (0.05, 1.23); p = 0.033]. for dilmapimod with overall reduction of 0.62 [95% CI (0.14, 1.10].	"The data from this exploratory cross-over trial show that the novel p38 MAPK inhibitor dilmapimod was associated with a significant reduction in pain intensity in patients with neuropathic pain following nerve injury. Although the findings require further investigation in larger parallel group studies, the data suggest that this class of compound may have the potential to be developed as novel treatments for neuropathic pain."	Crossover trial, data suggest dilmapimod was associated with significant pain reduction in NP pain.
Ostenfeld, 2013 (score=5.5)	Anti-inflammatories Losmapimod	RCT	Sponsored by Neurosciences Centre of Excellence for Drug Discovery,	N=168 subjects with pain	Mean age: 52 years; 63 males, 105 females	Losmapimod group (n=87): received 7.5 mg BID vs Placebo Group (n=81):	4 weeks	Mean change in PI-NRS score was -1.04 units for losmapimod group compared to -0.81	"Losmapimod could not be differentiated from placebo in	Quasi-randomization, data suggest comparable in efficacy

			GlaxoSmithKline R&D, Harlow. Study design, operational conduct, data analysis and manuscript preparation were undertaken by GSK. COI: The authors Thor Ostenfeld, Alok Krishen, Robert Lai, Jonathan Bullman, Amanda Baines, Joanne Green and Madeline Kelly were salaried employees and shareholders of GSK at the time of the study. Imperial College London received financial support from GSK to fund the investigation.			received at least one dose of study medication		units for placebo group. Mean treatment difference for the change in average daily pain score of treatment based on the PI-NRS was -0.22 (95% CI -0.73, 0.28) in losmapimod compared to placebo (p = 0.39).	terms of a primary analgesia response in patients with pain following peripheral nerve injury. The lack of response could reflect inadequate exposure at central sites of action or differences between rodent and human with respect to the target or neuropathic pain mechanisms.”	between losmapimod and placebo for NP pain following peripheral nerve injury.

NSAIDS & COX-2 Inhibitors

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Shackelford, 2009 (score=4.5)	GW406381	RCT	Sponsored by GlaxoSmithKline, Research Triangle Park, North Carolina. COI: S.S., R.H., and R.P. are employees of GlaxoSmithKline (GSK) and own GSK stock and/or stock options; R.R. has been a consultant for GSK; D.B. and S.Q. were full-time GSK employees at the time the study was conducted; and S.Q. holds GSK stock and stock options and has paid contractual agreements with GSK as well as other pharmaceutical companies.	N=209 patients with postherpetic neuralgia (PHN)	Mean age: 68.5 years; 102 males, 107 females	GW406381 25 mg (n=72): vs GW406381 50 mg (n=71): vs Placebo (n=66)	7, 14, 21, and 28 days	Mean NRS pain scores ranged from 5.9 to 6.6. Average daily NRS score was –0.3 (95% CI: –0.9 to 0.3) for GW406381 50 mg and –0.5 (95% CI: –1.1 to 0.1) for GW406381 25 mg.	"To our knowledge, this is the first report of a randomized, controlled clinical trial of a selective or nonselective COX inhibitor in neuropathic pain. The results of this study were inconclusive regarding the clinical relevance of the role of COX-2 in modulation of the symptoms of PHN."	Data suggest a trend forwards efficacy from either dose of GW406381.
Shihab, 2015 (score=4.5)	Topical NSAID lotion/cream	RCT	Sponsored by an investigator-initiated research proposal funded by Covidien,	N=28 subjects	Mean age: 48.8 years; 12 males, 16 females	Group A (n=14): received 1.5% diclofenac lotion vs Group B	5 weeks	Group A showed lower VAS scores after 2 weeks of 4.9±1.9 compared	"The findings indicate that 1.5% TD may serve as an effective treatment option	Crossover study, Data suggest modest trend in pain relief from

			Minneapolis, Minnesota. No COI.			(n=16): received placebo		to placebo of 5.6±2.1 (p=0.04).	for patients with neuropathic pain from postherpetic neuralgia and complex regional pain syndrome."	diclofenac group.

Corticosteroids

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Dureja, 2010 (score=6.5)	Prednisolone and Benzodiazepams and Midazolam	RCT	No COI or sponsorship.	N=150 patients with pain and allodynia	Mean age: 57.4 years; 79 males, 66 females	M-O (n=49): received methylprednisolone (60mg) suspended in 10 mL of normal saline in the epidural space and preservative free normal saline 2 mL in the intrathecal space vs M-1 (n=48): received normal saline 10 mL in the epidural space and midazolam 2 mL (1 mg/mL) in the intrathecal space vs M-2 (n=48): received methylprednisolone (60mg) suspended in 10	12 weeks	Groups M-1 and M-2 patients reported better pain relief compared to M-O group. M-2 Group showed better scores of pain and allodynia compared with patients M-O and M-1.	"The combination of intrathecal midazolam with epidural methylprednisolone resulted in prolonged duration of analgesia in patients with post herpetic neuralgia of lumbosacral dermatomes due to the complementary anti nociceptive action of intrathecal midazolam with epidural methylprednisolone on spinal nerve roots."	Data suggest combining epidural methyl prednisolone with intrathecal midazolam prolonged the analgesic effect in post herpetic neuralgia and decreased other analgesic use.

						mL normal saline in the epidural space plus midazolam 2 mL (1mg/mL) in the intrathecal space				
Van Wijck, 2006 (score=4.5)	Epidural Steroids	RCT	Sponsored by a grant from the Netherlands Organisation for Scientific Research (NOW number 945-02-009). No COI.	N=598 patients with acute herpes zoster	Mean age: 66 years; 234 males, 364 females	Epidural group (n=301): received standard therapy with one additional epidural injection of 80 mg methylprednisolone acetate and 10 mg bupivacaine vs Standard Group (n=297): received oral antivirals and analgesics	1, 3, 6 months	After 1 month of treatment, 137 patients in epidural group reported pain and 164 patients in standard group reported pain (p=0.02). After 3 months of treatment epidural group had 58 patients with reported pain and standard group with 63 patients (p=0.47). After 6 months, epidural group reported pain by 39 patients and standard group reported 44 patients (p=0.43).	"We conclude that one epidural injection of methylprednisolone and bupivacaine, applied in the acute phase of herpes zoster, has a modest effect in reducing zoster-associated pain for 1 month."	Standard care bias, data suggest only a modest effect from a single epidural injection of methylprednisolone plus bupivacaine vs standard care.

Dextromethorphan

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Grace 1998 (score = 8.0)	Dextromethorphan	RCT	Sponsored by Algos Pharmaceuticals. No mention of COI.	N = 37 scheduled for laparotomy for various causes, mostly cancer and inflammatory bowel diseases	Age range 25-75 years. Sex: unknown.	Dextromethorphan (DM) 60mg night before surgery and 1 hour before surgery (n = 18) vs. placebo (n = 19).	4 and 24 hours	Intraoperative morphine use lower in DM group. Total morphine sulfate use trended towards increased use 1st 24 hours. Intraoperative morphine use: dextromethorphan (13.1±1.0) vs. placebo (17.6±1.4), p = 0.012. NS between groups at all other times.	"[T]he preemptive use of 60mg of oral dextromethorphan given the night before and again an hour before surgery reduces intraoperative, but not postoperative, morphine requirements."	Small numbers. Procedures differed between patients. No post-operative differences noted in analgesic use.
Heiskanen 2002 (score = 8.0)	Dextromethorphan	Crossover Trial	Funded by the Helsinki University Hospital Research Funds (TYH9111). No mention of COI.	N = 20 with chronic pain >6 months	Mean age: 51.5 years; 15 males, 5 females.	Oral dextromethorphan 100mg PO (n = 10) vs. placebo 4 hours prior to IV morphine 15mg (n = 10) (5mg over 2 minutes, then 10mg in 1 hour).	Follow up 1-2 weeks.	No significant differences between groups.	"[O]ral dextromethorphan 100mg had no effect on pain relief by intravenous morphine 15 mg in patients with chronic pain."	Small numbers. All patients received IV morphine. Pain syndromes varied from CLBP to post-stroke central pain.

McQuay 1994 (score = 7.5)	Dextrometh orphan	Crossover Trial	No mention of sponsorship or COI.	N = 21 with chronic neuropathic pain, most (n = 13) post-surgical neuralgia or post-stroke pain	Mean age: 54.9 years; 14 males, 7 females.	Two 10-day treatments of dextromethorph an 13.5mg TID vs. placebo TID.	Follow up at 10 days.	Authors found no long-term clinical benefit in patients who continued with open DM.	"Dextromethorpha n at either 40.5 or 81mg daily did not relieve neuropathic pain."	Small numbers. Active drug 1 day and placebo next day for 10 days. Co-interventions not well controlled. Both central and peripheral lesions included.
Sang 2002 (score = 7.0)	Dextrometh orphan	RCT	Supported by project No. ZO1-DE00366 from the National Institute of Dental and Craniofacial Research Intramural, Bethesda, Maryland. Merz & Company, Frankfurt, Germany, provided memantine powder. No mention of COI.	N = 45 with painful diabetic neuropathy (DN, n = 23) and post-herpetic neuralgia (PHN, n = 22)	Mean age: 62 years; 24 males, 21 females.	Maximally tolerated dextromethorph an (DM): high and low dose, 100 and 300mg up to 960mg daily, vs. memantine: high and lose doses 6.0 and 1.8mg to 58mg daily vs. lorazepam: high and low doses 0.2 and 0.06mg to 2mg daily. Doses titrated over 7 weeks, then 2-week maintenance period. Medications 4 times daily.	Follow up every 2 weeks.	In final week, pain intensity scores for DN patients: DM 8.2±0.88 vs. 9.9±1.1 memantine vs. 10.1±1.2 lorazepam. Pain relief borderline significant for DM diabetics, but not memantine. Full-dose dextromethorphan treatment reduced pain more than lorazepam, p = 0.027; lower doses did not.	"Dextromethorpha n is effective in a dose-related fashion in selected patients with DN. This was not true of PHN, suggesting a difference in pain mechanisms. Selective approaches to pain-relevant N-methyl-D-aspartate receptors are warranted."	Sedation rates: DM 71% vs. memantine 63% vs. lorazepam 38%. GI adverse effects also different (17% vs. 0% vs. 0%).
Galer 2005 (score = 6.0)	Dextrometh orphan	RCT	No mention of sponsorship or COI.	Total (N=828). Trial 1: 327/Trial 2:	Mean age: 52.8 years; 542 males,	First trial morphine (MS)/DM	Follow up at 3 months.	Average daily MS dose 133mg a day for MS/DM group	"[A]dding the NMDA antagonist, dextromethorphan	Dropout rates ranged from 36 to 59%. Data

				308/Trial 3: 193	286 females.	15/15mg capsules (n = 160) vs. MS 15mg capsules (n = 167) for 7-21 days (327 patients). Second 308 OA patients, comparing MS/DM 15/15mg (n = 100) vs. MS/DM 15/7.5mg capsules (n = 107) vs. MS 15mg capsules (n = 101) with primary aim to assess MS dose-sparing by DM for 7-21 days. Third trial compared MS/DM 15/15mg capsules (n = 96) vs. MS 15mg capsules (n = 97) to assess MS dose-sparing by DM for 7-21 days.		vs. 125mg for MS (trial 1) Average daily pain intensity (baseline/last 7 days): MS/DM (3.1±1.08/3.8±1.60) vs. MS 15 (3.3±1.03/4.0±1.69) , p = 0.446. Average morphine dose was 69 vs. 71 vs. 74mg (trial 2). Average daily pain intensity: MS/DM 1:1 (3.2±1.2) vs. MS/MD 2:1 (3.1±1.3) vs. MS (3.5±1.3). Average MS dose was 134mg for MS/DM vs. 127mg for MS (trial 3). Average daily pain intensity: MS/DM 1:1 (3.9±1.3) vs. MS (4.1+1.2), p = 0.596.	, to opioids does not add any clinical benefit."	suggest lack of efficacy.
Katz 2000 (score = 6.0)	Dextrometh orphan	RCT	No mention of sponsorship or COI.	N = 89 (Trial 1) with chronic pain (17% cancer patients, remainder "other	Mean age: 52 years; 46 males, 43 females.	First double-blind crossover trial 2 of 2-weeks duration comparing combination agent with MS	Follow up at 2 weeks.	Capsules per day nearly identical, but combination agent appeared to lengthen time between doses. Daily MS nearly	"MS:DM provides satisfactory pain relief but at a significantly lower morphine daily dose."	Study details sparse. Adverse effects of dextromethorph an appear to be present, with increased

				causes" not well described); N = 185 (Trial 2) 25% with cancer, 75% "other causes")		alone dependent on patient need. MS:DM 15:15mg vs. MS 30mg. Doses titrated up or down to control pain. Second study 4-week RCT to ascertain effective doses among 185 patients. MS 30mg vs. MS:DM 30:30mg. Doses titrated up or down to control pain.		twice combination group. A 2-week run-in phase included (Trial 1). Daily dose of MS (mg): MS:DM 80.3±30.9 vs. MD 161.5± 53.3, p <0.0001. Number of doses per day: MS:DM 3.58±1.08 vs. MS 3.73± 1.06, p = 0.04. Capsules per day NS. Mean time (hours) between doses: MS:DM 6.99±3.6 vs. MS 6.42±2.2, p = 0.05. Mean time (hours) since last dose of day to 1st dose of next day: MS:DM 9.83±4.6 vs. MD 8.90±3.2, p = 0.01. Both groups achieved satisfactory control (78% vs. 80%). Randomized to MS group increased mean daily MS dose to greater degree than combination agent (16mg vs. 1.6mg) (Trial 2). Mean daily dose of morphine at Week 4: MS:DM 193 vs. MS 217, p = 0.044.		nausea, but reduced constipation.

Wu 1999 (score = 5.0)	Dextromethorphan	RCT	Supported by grants from the National Science Council (NSC 86-2314-B-016-071) and National Health Research Institute (DOH 87-HR-402) of Taiwan, Republic of China. No mention of COI.	N = 90 with ASA physical status 1-2 undergoing laparoscopic cholecystectomy	Mean age: 52.8 years; 50 males, 40 females.	Post-op DM 40mg IM (group A, n = 30) vs. preincisional DM 40mg (group B, n = 30) vs. standard chlorpheniramine maleate 20mg IM (control group, n = 30) also administered to other 2 groups.	Follow up at 2 days.	Meperidine consumption (mg): control 90.7± 65.2 vs. Group A 77.5±69.6 vs. Group B 20.0±24.1, p <0.00001. Group B vs. Group A, p <0.0000001. Worst pain scores: control 6.0±1.1 vs. Group A 6.0±1.1 vs. Group B 4.0±2.2, p<0.0001 group B vs. Group A, p <0.000001 Group B vs. control. Bed rest time (h): control 21.0±2.7 vs. group A 20.0±2.7 vs. Group B 19.0±2.2, p <0.001 group B vs. Group A and control. Meperidine-related side effects: control 7 vs. Group A 6 vs. Group B 3. Meperidine requirement: control 26 vs. Group A 22 vs. Group B 12, p <0.05 Group A vs. control, p <0.005 Group B vs. Group A and control.	"Preincisional dextromethorphan (40 mg IM) treatment offers a preemptive analgesic effect, thus improving the postoperative pain management."	No mention of other pain syndrome, psychological diagnosis in baseline characteristics. Adverse events not well described.

Immune Modulators (Isoprinosine, Cimetidine)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Payne, 1989 (score=4.0)	Isoprinosine	RCT	No mention of sponsorship or COI.	N=38 patients with acute herpes zoster	Mean age:70 years; 20 males, 18 females	Isoprinosine group (IP) (n=19): vs Placebo group (n=16):	2 weeks, 1, 2, 3 months	IP did not shorten phase of HZ and did not prevent postherpetic neuralgia. One-third of IP group was affected by transient asymptomatic hyperuricaemia.	"(i)soprinosine does not influence the natural history of herpes zoster in the elderly."	Data suggest lack of efficacy.

Cizolirtine Citrate (E-4018)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Shembalkar, 2001 (score=4.5)	Cizolirtine Citrate	RCT	Sponsored by Laboratories Dr Esteve SA, AV. Madre de Dèu de Montserrat, 221-08041 Barcelona, Spain. No mention of COI.	N=25 patients with neuropathic pain	Mean age: 49.5 years; 13 males, 12 females	Cizolirtine citrate: received 200 mg twice daily for 21 days vs Placebo: received same dosing with placebo capsules	1, 7, 14, 21 days	Mean VAS score with cizolirtine at rest (39.7 ± 22.3 mm, p = 0.04), and on movement (46.4 ± 24.9 mm, p = 0.02). Mean VAS with placebo were (rest: 40.0 ±22.9 mm, p > 0.22; movement: 47.2±25.2 mm, p > 0.48). Thirty percent reduction in pain intensity was achieved by both groups ≥40% of patients.	"Cizolirtine may be effective in primary allodynia after peripheral nerve injury, and a further trial in a larger number of such subjects is warranted."	Data shows a slight trend towards E-4018 vs placebo in the treatment of chronic neuropathic pain.

NNR (ABT-894)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Rowbotham, 2012 (score=4.5)	ABT-894	RCT	Sponsored by Abbott Laboratories. Dr. Rowbotham has served as a consultant to Abbott, Adynxx, Afferent Pharmaceuticals, Allergan, Arcion, Bristol Meyers Squibb, Cardiome, Flexion, Kyowa Hakko Kirin, Neurotherapeutics Pharma, Nuvo Research, Xenon, Xenoport, and Zalicus. COI: Dr. Stacey has received grant support from NeurogesX and Pfizer, and has served as a consultant to AstraZeneca, Boehringer Ingelheim, Endo Pharmaceuticals, NeurogesX, and Pfizer. Dr. Arslanian has no conflicts of interest to declare. Dr. Zhou is an employee of Abbott. Drs. Nothaft, Duan, Best, and Pritchett are employees of Abbott and hold Abbott stock and stock options.	N=404 with painful distal symmetric diabetic polyneuropathy for ≥6 months	Mean age: 58.1 years; 224 males, 180 females	Study 1: ABT-894 (1 mg, 2 mg, 4 mg) vs Duloxetine (60 mg) vs placebo Study 2: ABT-894 (6mg, 4 mg)	1, 2, 4, 6, 8, 9 weeks	For both trials, none of ABT-894 dose groups showed success compared with placebo (Study 1: P≥.457; study 2: p=.347).	"The failure of the highly selective a4b2 NNR agonist ABT-894 indicates that it may not be possible to define a therapeutic index for this mechanism or that selectively targeting a4b2 NNRs may not be a viable approach to treating neuropathic pain."	Data suggest lack of efficacy.

Sierra, 2015 (score=4.0)	AT-639	RCT	This study was sponsored by AbbVie Inc. AbbVie was involved in the study design, collection and interpretation of data, and writing, reviewing, and approving the manuscript. Authors are employeed and hold stock in Neuroscience technologies, AbbVie, Abbott, and Shire.	N=39 patients diagnosed with diabetes mellitus type 1 or 2 with clinical evidence of diabetic neuropathy.	Mean Agefor ABT group 50.6±14.3, Lidocaine group 51.1±13.2, Placebo group 53.4±14.1; 26 Males, 13 Females.	Group 1, (ABT-639) received a single dose (orally) of 100 mg and placebo IV for 30 min. (N=19) vs. Group 2, Lidocaine, received oral placebo and 3 mg/kg IV for 30 min. (N=10) vs. Group 3, Placebo, which received oral glucose and IV glucose for 30 min. (N=10)	Blood samples taken at 0.5, 0.75, 1, 1.5, 2, 3, and 4 after oral ingestion. Microneurography measures taken every ten minutes after oral dose. Pain intensity taken every hour for 4 hours.	There were no differences in the pain intensity between all three groups. 6/39 individuals reported adverse event most prominent was dizziness.	"[N]o statistically significant improvements in spontaneous activity were observed between ABT-639 100 mg and placebo, and there were no meaningful differences in pain intensity scores. Similar findings were observed for lidocaine 3 mg/kg vs placebo."	Data suggest comparable (in) efficacy.

CCR2 Antagonists

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kalliomäki, 2013 (score=7.0)	CCR2	RCT	Sponsored by AstraZeneca R&D. COI: J. Kalliomäki, B. Jonzon, K. Huizar and B. Eriksson are employees of AstraZeneca R&D Södertälje. N. Attal, F.W. Bach, S. Ratcliffe, A. Danilov and D. Bouhassira are consultants for AstraZeneca R&D. M. Janecki has no conflict of interest to report.	N=133 patients with posttraumatic neuralgia	Mean age: 53.1 years; 71 males, 62 females	AZD2423: received 20 mg vs AZD2423: received 150 mg vs Placebo	36-43 days	Mean change in NRS-average pain score was -1.54 for AZD2423 20mg group, -1.53 for AZD2423 150 mg group, and -1.44 for placebo group.	"The CCR2 antagonist AZD2423 demonstrated no efficacy on NRS average pain scores and most of the secondary pain variables. The NPSI data suggested possible effects on certain sensory components of pain. There were no major safety or tolerability concerns."	Data suggest AZD2423 demonstrated analgesic efficacy on pain scores and most secondary variables for treatment of PTN.

Magnesium

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Pickering, 2011 (score=4.0)	Magnesium	RCT	Sponsored by French Ministry of Health Regional PHRC and no COI.	N=45 patients with neuropathic pain	Mean age: 53±11 years; 22 males, 23 females	Treatment A: received Magnesium chloride (Mg) 419 mg vs Treatment B: received lactose 6 tablets per day	28-31 days	Total NPSI score between placebo and magnesium was p=0.8569. Mean NS pain and maximal NS pain between placebo and magnesium were p=0.6295; p=0.7460.	"This randomised clinical trial could not demonstrate any significant difference in pain scores between oral Mg and placebo in 45 patients suffering from neuropathic pain. A large placebo response was observed with an improvement of all patients in pain report and quality of life. This study contrasts with previous preclinical results but may suggest an influence of Mg on pain paroxysms and affective functions. Frequency of pain paroxysms, emotional impact and their relationship will be studied further, in human and in animals, as they constitute major aspects of pain alleviation in chronic pain conditions."	Data suggest both treatment and placebo groups improved showing (in) efficacy of magnesium for NP pain.

Kim, 2015 (score=4.0)	Magnesium sulfate	RCT	No mention of sponsorship or COI.	N=30 patients with severe, intractable PHN	Mean age: 69 years; 9 males, 21 females	Ketamine group (n=15): received 1 mg/kg diluted by 0.9% saline to total 100 mL for 3 sessions every other day vs Magnesium group (n=15): received 30 mg/kg diluted with 0.9% saline intravenously for 1 hour for 3 sessions every other day	2 weeks	VAS score after treatment for ketamine group was 4.33±2.15 and 3.1±1.45 for the magnesium group (p<.001). Mean pain reduction value was 51% for ketamine group and 39.6% for magnesium group.	"Ketamine and magnesium showed significant analgesic effects in patients with PHN."	Data suggest comparable efficacy for pain reduction between groups.

Topical Creams

Lynch, 2005 (score=7.0)	Amitriptlyine, Ketamine	RCT	Sponsored by Epicept Corporation, Englewood Cliffs, New Jersey. COI: Dr. Sawynok holds a patent for topical antidepressants(other than amitriptyline) as analgesics (US patent No. 6,211,171).	N=92 patients with diabetic neuropathy, postherpetic neuralgia, or postsurgical/posttraumatic neuropathy pain with allodynia, hyperalgesia, or pinprick hypesthesia	Mean age: 52.5 years; 47 males, 29 females	2% Amitriptyline (n=22):, 1% Ketamine (n=22), 2% Amitriptyline-1% Ketamine (n=23): vs Placebo (n=25):	2, 3 weeks	ANOVA NRS-PI scores effect for time was F3,264 = 27.2, $P < 0.001$. Treatment NRS-PI scores were F3,88 =1.3, $P = 0.27$ and interaction was F9,264 =0.25, $P = 0.95$.	"This randomized, placebo-controlled trial examining topical 2% amitriptyline, 1% ketamine, and a combination in the treatment of neuropathic pain revealed no difference between groups. Optimization of doses may be required, because another study has revealed that higher concentrations of these agents combined do produce significant analgesia."	Data suggest comparable in efficacy in all 4 groups.

Kulkantrakorn 2012 (score=5.5)	Topical capsaicin	RCT	Sponsored by Research Grant from Faculty of Medicine, Thammasat University and Bangkok Drug Company Ltd. No COI.	N = 33 patients with diabetic neuropathy.	Mean age is 58 years. 16 males, 17 females.	Topical capsaicin 0.025% gel Group (N=16) vs. B Placebo Group (N=17).	8,12, and 20 weeks.	There was no improvement of pain with the capsaicin gel, compared with placebo (VAS score 28.8 mm vs. 34.6 mm; P=0.53).Pain relief of 30% was observedin 27.3% and 30.3% of patients with capsaicin and placebo respectively (P=0.786). 50% improvement was seen in 18.2% patients with capsaicin and 27.3% patients with placebo (p=0.378)	"Topical preparation of capsaicin at 0.025% concentration provided no significant benefit in providing pain relief in patients with PDN."	Crossover study with small sample and high dropout rate. Data suggest lack of efficacy.
McCleane, 2000 (score=4.5)	Topical Capsaicin vs Doxepin	RCT	No mention of sponsorship or COI.	N = 151 individuals with chronic, neuropathic pain.	Mean age: Doxepin group 47.8, Capsaicin group 47.8, Doxepin + Capsaicin group 43.6, and Placebo group 45.4 Sex(M:F) 63:88	All groups applied a small volume of cream to the painful area 3x each day for 4 weeks. doxepin group (N=41), capsaicin group (N=33), doxepin/capsaicin group (N=36), placebo group (n=41)	Week 4	Overall pain was unchanged in the placebo group, but fell by 0.9 in the doxepin group (p<0.001), 1.12 in the capsaicin group (p<0.001) and 1.07 in the doxepin/capsaicin group (p<0.001). The results also show the duration of pain in the doxepin/capsaicin group was greater than the other groups (P=0.05).	"In conclusion, the topical application of 3.3% doxepin hydrochloride, 0.025% capsaicin and 3.3% doxepin/ 0.025% capsaicin is associated with analgesia in chronic human neuropathic pain. The extent of analgesia is similar in each group, but is more rapidly achieved with the doxepin/capsaicin combination. 0.025% capsaicin had a marked effect on sensitivity and a lesser effect on shooting pain. Burning pain is increased by doxepin, capsaicin and doxepin/capsaicin, although in the latter group the rise in burning pain is less substantial."	Data suggest comparable efficacy for all groups compared to placebo with the combination cream acting faster Type of neuropathy not well describedCapsaicin.

Teixeira, 2014 (score=4.0)	Topical Capsaicin (lipsosomal)	Pilot study	No COI and sponsored by InVitro Phamacia de Manipulacão for their preparation of the active and placebo creams.	N=19 patients with neuropathic pain secondary to PHN	Mean age: 71.94±10.5 years; no mention of sex	Capsaicin group (n=: received 0.025% liposomal capsaicin for 6 weeks applied 2-3 times per day vs Placebo group: received placebo applied 2-3 times per day for 6 weeks	2, 4, 6 weeks	Mean duration of pain was 33.4±21 months. VAS score ranged from 7±2.17 to 5.31±2.65 for capsaicin compared to placebo with 6.38±2.5 to 6±2.64 (p=0.008 for time, p=0.076 for treatment).	"(l)iposomal capsaicin was safe and well tolerated. At the concentration used, its analgesic effects were marginal and not significant. This was a pilot, safety study assessing the effects of lipossomal capsaicin as an ad-on treatment to patients already taking at least two different types of medication. We suggest that higher concentrations of liposomal capsaicin should be tested in larger studies of PHN patients to determine its clinical efficacy."	Crossover design, small sample pilot study, data suggest a trend towards efficacy.
Bernstein, 1989 (score=4.0)	Topical capsaicin	RCT	Sponsored by grants (FD-R-000072-02-1 and FD-R-000072-02-2) from the Department of Health and Human Services, the U.S. Food and Drug Administration, and GenDerm Corporation, Northbrook, Illinois. No mention of COI.	N=32 patients with history of severe intractable postherpetic neuralgia	Mean age: 72.5 years; 12 males, 20 females	Capsaicin group (n=16): vs Vehicle group (n=16):	6 weeks	Seventy-seven percent of capsaicin group showed reduction in pain compared to placebo group with 31% at follow-up (p< 0.05). VAS pain score for capsaicin group at baseline was 71.0 mm and 71.5 for placebo. Capsaicin group showed 30% mean decrease in VAS compared to placebo with a 1% increase in score (p<0.05).	"The present double-blind, vehicle-controlled study demonstrates that topically applied capsaicin provides partial to complete relief from pain in nearly 80% of patients with chronic intractable postherpetic neuralgia."	Data suggest capsaicin provides pain relief up to 6 weeks.

Low, 1995 (score=4.0)	Capsaicin cream	RCT	Sponsored by grant-in-aid by GalenPharma, Northbrook, Illinois. No mention of COI.	N=39 patients with chronic distal painful polyneuropathy	Mean age: 59 years; 24 males, 16 females	CAPS group: received capsaicin cream 4 times per day vs PLAC group: received methyl nicotinate placebo	4, 8, 12 weeks	Median QSART sweat volumes for CAPS at baseline, 4 and 8 weeks were 1.00, 0.64 and 0.71 µl/cm² compared to placebo of 0.77, 0.61 and 0.66 µl/cm². Neurogenic flare response did not change as a result of treatment.	"We interpret the early hyperalgesia on the CAPS side as being responsible for the better performance of PLAC at early time points. The large percentage of limbs that improved may be a pronounced PLAC response."	Data suggest lack of efficacy.
Mahoney 2012 (score=4.0)	Ketamine cream	RCT	Funded by a grant from the Des Moines University Investigational Osteopathic Education and Research Grants. No COI.	N = 17 patients with diabetes.	Mean age is 64.7 years. 8 males, 9 females.	1 mL of ketamine cream (N=10) vs. 1 mL of placebo cream (N=7)	18 months.	Diabetic pain measures were reduced in all seven of the pain characteristics. Placebo is equally as strong as 5% topical ketamine.	"The 5% topical ketamine cream was no more effective than was placebo in relieving pain caused by diabetic neuropathy"	Small sample. Data suggest lack of efficacy.
McQuay, 1989 (score=4.0)	Benzydamine Cream	RCT	Sponsored by pain research funds and no mention of COI.	N=23 patients with post-herpetic neuralgia	Mean age: 73±2 years; 4 males, 19 females	Benzydamine group: received benzydamine hydrochloride 3% vs Placebo Group: received 80% aqueous cream, 10% Ung Merck	6 weeks	AUC diary scores for pain intensity were lower for wash-out period compared with run-in period (10±1 vs 12±0.8; p=0.03). Order effect was detected in AUC pain scores were higher for in 1st week instead of 2nd week of treatment (17.9±2.4 vs 9.7±1.3; p=0.002).	"(o)nly interpretation of these results is that there was no benefit from the topical anti-inflammatory compared with placebo in 2-week treatment periods."	Crossover study, 2 week treatment period, data suggest lack of efficacy.

Topical Lotions

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ahmed 2015 (score=4.5)	Topical NSAID lotion/cream	RCT	Sponsored by an investigator-initiated research proposal funded by Covidien, Minneapolis, Minnesota. No COI.	N=28 subjects	Mean age: 48.8 years; 12 males, 16 females	Group A (n=14): received 1.5% diclofenac lotion vs Group B (n=16): received placebo	5 weeks	Group A showed lower VAS scores after 2 weeks of 4.9±1.9 compared to placebo of 5.6±2.1 (p=0.04).	"The findings indicate that 1.5% TD may serve as an effective treatment option for patients with neuropathic pain from postherpetic neuralgia and complex regional pain syndrome."	Crossover study, Data suggest modest trend in pain relief from diclofenac group.

Topical Suspensions

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
De Benedittis, 1991 (score=5.0)	Topical ASA suspension Vs Diclofenac vs Placebo	RCT	No mention of sponsorship or COI.	N=45 patients with acute herpetic neuralgia (AHN) and post-herpetic neuralgia (PHN)	Mean age: 61.6 years; 20 males, 25 females	Group A: received aspirin, diethyl ether vs Group B: received indomethacin, diethyl ether vs Group C: received diclofenac, diethyl ether vs Group D: received placebo of lactose with diethyl ether	4 weeks, 2-24 months	For open-pilot study, mean VAS score for AHN group was 5.8±1.8 and for PHN group was 5.8±1.4. For RCT, mean pain reduction for group A was 69.2±9.7, 59.4±10.8 for group B, 55±10.4 for group C, and 23.3±10 for group D. Mean pain relief was 281±68 for group A, 178±42 for group B, 283±81 for group C, and 44±19 for group D.	"In conclusion, ADE has proved to be a new, practical, safe and highly efficient treatment for AHN and PHN. Moreover, it seems to lower dramatically the risk of developing this intractable, painful complication. For these reasons, we recommend it as a first choice treatment."	Open label, trial then secondary pilot RCT, data suggest aspirin/diethyl ether accelerated lesion healing and suppressed some disease severity. Also, patients using above treatment developed less PHN. In the second pilot RCT, ASA was clinically superior for pain relief.

De Benedittis, 1996 (score=4.5)	Topical ASA suspension	RCT	No mention of sponsorship or COI.	N=37 patients with AHN or PHN	Mean age: 70.9 years; 15 males, 22 females	All patients received 4 sessions of each topica agent. ASA group: received diethyl ether and aspirin vs IND group: received indomethacin and diethyl ether vs DIC group: received diclofenac and diethyl ether vs PLA group: received placebo of lactose and diethyl ether	None	All mean pain intensity VAS scores for AHN after ADE measure were improved from 6.2±0.5 to 2.4±0.5 ($p<0.01$). All mean pain intensity VAS scores for PHN after ADE topical application improved from 6.4±0.3 to 2.2±0.5 ($p<0.01$).	"On the whole, patients with trigeminal involvement, less severe pain and with dysaesthetic quality of pain yielded best results."	Crossover study, data suggest the best responders to topical ASA/diethyl ether were those with less severe pain involving the trigeminal region.

Capsaicin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Backonja, 2008 (score=6.5)	Capsaicin Patch	RCT	Sponsored by NeurogesX. COI:MB was reimbursed by NeurogesX for his roles as principal investigator and adviser to the development of the protocol, and for contributing patients. MSW has received financial	N=402 patients with PHN	Mean age: 71.1 years; 190 males, 212 females	NGX-4010 (n=205): patch was applied for 60 minutes vs Control (n=197):	4, 8, and 12 weeks	Greater reduction in NPRS score was observed for NGX-4010 group compared to control group ($p=0.002$). Mean changes in NRPS score were -29.6% vs -19.9%.	"(o)ne 60-min application of NGX-4010 resulted in a rapid and significant reduction in pain that was sustained for up to 12 weeks in patients with PHN. Reductions in pain were seen when NGX-4010 was used alone and in	Single patch application and removal, data suggest a high concentration capsaicin patch was significantly effective for treatment of PHN for up to 12 weeks.

			research support from NeurogesX. ERB is a principal investigator on research trials sponsored by Abbott, Allergan, Astellas, Bristol-Myers Squibb, Eisai, Endo, Lilly, NeurogesX, Pfizer, Schwarz,Takeda, and Wyeth; he is on the speakers' bureaus for Cephalon, Endo, Lilly, and Pfizer; andhe sits on advisory oards for Abbott, Endo, and Lilly. BJC and RR have been principal investigators on clinical trials funded by NeurogesX. PM has been an investigator on trials funded by NeurogesX. JT is an employee of NeurogesX.						combination with other neuropathic pain medications."	
Irving, 2011 (score=6.5)	Capsaicin Patch	RCT	Sponsored by NeurogesX, Inc. COI: Gordon Irving and Misha Backonja are consultants for	N=418 patients with postherpetic neuralgia	Mean age: 70.3 years; 190 males, 226 females	NGX-4010 (n=212): received 60 minute application of	12 weeks	Treatment group showed a mean reduction of pain of 32.0±2.07% compared with control group with	"In patients with PHN, a single 60-minute application of NGX-4010 produced significant reduction	Phase III study, data suggest efficacy with a single high concentration

			NeurogesX. Jeffrey K. Tobias and Geertrui F. Vanhove are NeurogesX employees ad own NeurogesX stock. Shiao-Ping Lu is a former NeurogesX employee and owns NeurogesX stock. No other COI for remaining authors.			NGX-4010 vs Control group (n=204): received 0.04% capsaicin patch (3.2 mg/cm2)		24.4±2.11% (p=0.011). Decrease in pain score of ≥50% was greater for NGX-4010 group (29% vs 20%, p=0.04).	in pain that was maintained over a 12-week period."	capsaicin patch to reduce pain up to 12 weeks.
Webster, 2010 (score=6.0)	Capsaicin Patch	RCT	Sponsored by NeurogesX. COI: Lynn Webster is a consultant for Neurogesx. Jeffrey K. Tobias, and Geertrui F. Vanhove are NeurogesX employees and own NeurogesX stock.	N=299 patients with postherpetic neuralgia	Mean age:71.6±0.27 years; 112 males, 110 females	Group A (n=73): received NGX-4010 for 90 minutes vs Group B (n=77): received NGX-4010 for 60 minutes vs Group C (n=72): received NGX-4010 for 30 minutes vs Control (n=77):	4, 8, 12 weeks	Mean pain reduction observed for Groups A, B, and C were similar 27.8%, 25.6%, 26.2% respectively. Difference between group A and control wa p=.0438. Mean percent reduction in NRPS score was significantly greater for toal NGZ-4010 group (26.5%, p=0.0286) and the 90 minute group (27.8%, p=.0438) compared to placebo (17.3%).	"This randomized, double-blind, dose-finding study demonstrates that, in patients with PHN, a single application of NGX-4010 can provide pain relief that is maintained for up to 12 weeks following treatment."	Comparison of 30 min, 60 min, and 90 mi application, data suggest 60 minute application of NGX-4010 patch appeared to have the greatest amount of pain reduction.
Webster, 2010b (score=6.0)	Capsaicin patch	RCT	No mention of sponsorship and COI: LRW, MT and RR were compensated by NeurogesX for their roles as principal investigators. LRW and RR are consultants for Neurogesx and Astellas. JKT and	N=155 patients with postherpetic neuralgia	Mean age: 69.6 years; 72 males, 83 females	NGX-4010 (n=102): received cap-saicin 640 µg/cm2, 8% vs Control (n=53): received low-concentration capsaicin control patch (capsaicin	12 weeks	Patient reported reduction in pain was 36.5% for NGX-4010 group compared to placebo 29.9% (p=0.296).Post hoc analysis showed greater reduction in overall NRPS scores from baseline to 6 months compared to control	"Although treatment appeared to be safe and well tolerated, a single 60-minute application of NGX-4010 failed to show efficacy in this study which included patients with PHN for less than 6 months. Large reductions in	Single dose patch applied for 60 min, data suggest a trend towards efficacy in NGX-4010 vs placebo although not significant.

			GFV are employees of NeurogesX and own NeurogesX stock.			3.2 µg/cm0.04%)		group (37.6% vs 23.4%, p=0.0291).	pain observed among control patients with pain for less than 6 months may have been due to spontaneous resolution of PHN, may have confounded the results of the prespecified analyses, and should be taken into account when designing PHN studies.“	
Irving, 2012 (score=6.0)	Capsaicin patch	RCT	Sponsored by NeurogesX, Inc. COI: Drs Irving, Backonja, Rauck, and Webster are consultants for NeurogesX and Astellas. Dr Irving is part of the speaker’s bureau for NeurogesX and Astellas. Drs Tobias and Vanhove are NeurogesX employees and own NeurogesX stock.	N = 1127 with a diagnosis of post herpetic neuralgia (PHN) and an average Numeric Pain Rating Scale (NPRS) score of 3 to 9 and that their herpes zoster had elapsed for at least 6 months.	Mean age: 71 years; 537 males, 590 females	Treatment group: received NGX-4010 for 60 minutes once and continued to record their average pain during 24 hours for the next 12 weeks. The treatment group was stratified into those using systemic pain meds (N = 302) vs. not using systematic meds (N = 295) (N = 597) vs. The control group received	Both groups had clinic visits at a week 4, 8, and 12.	When compared to control patients, the NGX-4010 patients reported greater reductions in NPRS scores for those using systemic medication (-26.1% vs. -18.1, P = 0.0011) and those not (-36.5% vs. -26.2%, P = 0.0002).	"[A] single 60 minute NGX-4010 treatment reduces PHN for up to 12 weeks regardless of concomitant systemic neuropathic pain medication use".	Pooled Analysis, applications of 30 min, 60 min, 90 min, data suggest a one time single patch application of NGX-4010 followed by removal of patch either alone or in combination with other systemic NP pain medications reduces PHN up to 12 weeks.

						one treatment with patch made from (0.04% capsaicin patch) and also recorded their average pain intensity for 24 hours for 12 weeks. The control group was also stratified further by systemic pain meds (n=250) vs. those not on systemic meds (n=280) (N = 530).				
Clifford, 2012 (score=6.0)	Capsaicin patch	RCT	Sponsored by NeurogesX. COI: Dr. Vanhove is a former employee of NeurogesX, Inc. and currently holds stock in the company. Dr. J.K.T. is a former employee with stock in NeurogesX, Inc., Dr. G.F.V. holds stock in NuerogesX, Inc., and Dr. D.B. C., Dr. S.B. and Dr. B.C. have received grants from	N=494 patients with pain due to HIV-associated distal sensory polyneuropathy	Mean age: 49.7 years; 432 males, 62 females	Group 1 (n=165): received NGX-4010 capsaicin 8% patch for 60 minutes vs Group 2: received NGX-4010 capsaicin 8% patch for 30 minutes vs Group 3 (n=90): received placebo for 60 minutes vs Group 4 (n=72): received placebo for 30 minutes	4, 8, 12 weeks	Mean percent change in NRPS score for Groups 1 and 2 were -29.5% compared with Groups 3 and 4 with -24.5% (p=0.097). Pain reduction for Group 1 versus Groups 3 and 4 were -32.8% vs -30% respectively (p=.488).	"Although the primary endpoint analyses were not significant, trends toward pain improvement were observed after a single 30-minute NGX-4010 treatment."	Intervention with NGX-4010 was a single patch applied for either 30 min or 60 min, data suggest a modest trend towards pain improvement in NGX-4010 but not significant from 30 min treatment.

			NeurogesX, Inc. in the past.							
Jensen, 2014 (score=5.5)	Capsaicin patch	RCT	Sponsored by Astellas Pharma Europe Ltd. COI: T.S.J. has received honoraria for participation in advisory boards or speakers' bureaus for Astellas, Pfizer and Grunenthal. K.H. has received honoraria for oral presentations and participation in advisory boards from Astellas Pharma, AstraZeneca, Eli Lilly, MSD, Pfizer and Takeda Nycomed. J.F. has acted as a senior consultant and lecturer for Astellas Pharma Europe Ltd. P.V. has no conflicts of interest. E.E. is a consultant for Astellas Pharma Europe Ltd. T.S. and S.M. are employed by Astellas Pharma Europe Ltd.	N=122 patients with peripheral neuropathic pain	Mean age: 55.3±16.4 years; 52 males, 70 females	Capsaicin plus Lidocaine group (n=61):vs Capsaicin plus Tramadol (n=61):	None	Post treatment application showed pain level increase to 55 minutes. Mean changes in NRPS scores were 0 for lidocaine group and -1 for tramadol group.	"Capsaicin 8% patch tolerability was similar in the two arms, with comparable results for most secondary endpoints. Tramadol given 30 min before patch application should be considered as an alternative pretreatment option in patients receiving capsaicin patch treatment."	Data suggest comparable efficacy between 2 treatment groups for pretreatment with either lidocaine or tramadol.
Haanpää, 2015 (score=5.0)	Capsaicin patch vs Pregabalin	RCT	Sponsored by Astellas Pharma Europe Ltd. COI:	N=568 patients with peripheral	Mean age: 55.0 years; 245 males,	Capsaicin group (n=282):	4 weeks	Patients achieving a ≥30% decrease in mean NRPS score was 55.75	"The capsaicin 8% patch provided non-inferior pain relief to	Open label non-inferiority trial, data

			Professor Maija Haanp€a€a was principal investigator for the ELEVATE study. She has received honoraria from Astellas for speaking at sponsored meetings. Dr William McBride as a member of the independent data review board received a fee for service from Astellas. He was a speaker at an Astellas sponsored symposium on 7th October 2014 at IASP. Professor Giorgio Cruccu received a fee for service from Astellas as member of the Independent Review Board for the ELEVATE study. He has worked with Astellas, Convergence, Lilly and Pfizer. Professor Turo Nurmikko has received fees for service from Astellas for speaking and acting as Chairman of the Independent Review Board for the ELEVATE study.	neuropathic pain	314 females	received 640 lg/cm2 [8% weight for weight]) capsaicin patch vs Pregabalin group (n=277): received oral pregabalin		for capsaicin group and 54.5% for pregabalin group. Mean pain relief time was short for capsaicin group compared to pregabalin group, 7.5 days vs 36 days respectively (p<0.0001).	an optimized dose of pregabalin in PNP, with a faster onset of action, fewer systemic side effects and greater treatment satisfaction."	suggest capsaicin 8% patch performed quicker for pain relief than the oral pregabalin (7.5 days vs 36 days).

			Dr Bosilkov received financial remuneration from Astellas Pharma for participation in the ELEVATE study based on the study contract conditions. E Ernault, C Chambers, and A Abdulahad are employed by AstellasPharma Europe.							
Backonja, 2010 (score=4.0)	Capsaicin patch	RCT	Sponsored by NeurogesX. COI: Misha Backonja is a consultant for Neurogesx. Jeffrey K. Tobias and Geertrui F. Vanhove are NeurogesX employees and own Neuroges X stock. T. Philip Malan has no conflict of interest.	N=38 patients with postherpetic neuralgia	Mean age: 74.9 years; 15 males, 23 females	NGX-4010 group (n=26): received capsaicin (640 mg/cm2, 8%) vs Control (n=12): received low concentration capsaicin control patch (3.2 mg/cm2, 0.04%)	4 weeks	NGX-401 group showed decrease of 32.7% for NRPS mean scores compared with control group with 4.4% (p=0.003). BPI results change was -1.7 for NGX-4010 group compared to 0.3 for control group (p=0.014). BPI average pain changed -1.3 for NGX-4010 compared to control 0.4 (p=0.032).	"NGX-4010 is a promising topical treatment for PHN patients, which appears to be tolerable, generally safe, and effective."	Open label extension study, data suggest a high concentration capsaicin patch can maintain treatment benefits for up to 1 year.

Lidocaine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Galer 1999 (score = 9.0)	Lidocaine Patch	Crossover trial	Supported by a grant from Hind Health Care, Inc. No mention of COI.	N = 33 with PHN	Mean age is 77.4 years. 14 males, 18 females.	Five % lidocaine patches vs. placebo patches for 28 days.	Follow up 2 weeks.	Patches 3 times a day, 1 each wore 4-5 patches a day. Required to be responsive to lidocaine patches in open-label phase. Most preferred lidocaine patch (78.1% vs. 9.4%). More reported moderate or greater pain relief for at least 5 days using lidocaine patch.	"Topical lidocaine patch is a novel therapy for PHN that is effective, does not cause systemic side effects, and is simple to use."	Open-label phase may somewhat limit generalizability of study. Main outcome measure time to efficacy of decrease in pain score of "2" for 2 consecutive days which was stated in abstract to be greater than 14 days for lidocaine, 3.8 days for vehicle patch, thus data appear to be switched in abstract. Type of neuropathy not well described.
Demant 2015 (7.5)	Lidocaine Patch	Crossover RCT	Sponsored in party by the Innovative Medicines Initiative Joint Undertaking from the European Union's Seventh Framework	N = 46 with localized peripheral neuropathic pain	Median age: 59.5 years; 17 males, 23 females.	Patients initially split by phenotype then randomized: Irritable nociceptor (n = 19): lidocaine patch (n = 9) vs.	None.	Lidocaine patches reduced pain by 0.3 points (95% CI 0.1-0.5), pain-related sleep disturbance reduced by 0.6 points (95% CI 0.4-0.8). These were significant	"In conclusion, lidocaine 5% patch had an effect on peripheral neuropathic pain, and it may be most efficacious in patients with IN phenotype. The	Crossover trial. Data suggest lidocaine 5% patch provides better pain relief in the irritable nociceptor (IN) phenotype.

			Programme and EFPIA companies' in kind Contribution and by Grünenthal, Denmark APS. COI – one or more of the uathors have received or will receive benefits for personal or professional use.			placebo (n = 10) Non-irritable nociceptor (n = 27): lidocaine (n = 15) vs. placebo (n = 12) Each group received both treatments for a period of 4 weeks, with a 1 week washout period between. Lidocaine 5% patches with 700 mg lidocaine used, up to 3, used up to 12 hours/day followed by 12 hours without patches		compared to placebo (P = 0.007 and P < 0.001)	lack of significant phenotype differences may be caused by too low statistical power."	
Meier, 2003 (score=5.5)	Lidocaine Patch	RCT	Sponsored by IBSA (Pambio-Noranco, Switzerland). No mention of COI.	N = 40 patients with various forms and localizations of peripheral neuropathic pain syndromes (PNPS).	Mean age of group 1: 63.9, group 2: 66.7 Sex (M:F) 15:25	Group 1 (N = 20) received a lidocaine patch 5% and were instructed to use up to 4 patches for 12 hours daily for 7 days. A 7- or 14-day washout period followed. A second 7-day treatment period then commenced	Day 7 of lidocaine treatment period and 1 month.	Use of the lidocaine patch 5% effectively reduced ongoing pain (p=0.017) and allodynia (p=0.023) during the first 8 hours of use. In treatment of diverse focal PNPS the lidocaine patches worked significantly better than the placebo patch over a 7 day period (p=0.018)	"…the results of the present study show the strength of the lidocaine patch in the treatment of diverse focal PNPS. It can be used as a first line treatment and is also a perfect add-on therapy in a multidrug concept."	Crossover study, data suggest lidocaine patch 5% may be an appropriate adjunct therapy to treat focal peripheral neuropathic pain syndromes.

						using placebo patches. Group 2 (N = 20) used the same methods as group 1, but in reverse order.				
Galer 2002 (4.0)	Lidocaine Patch	RCT	No mention of sponsorship or COI.	N = 96 with postherpetic neuralgia	Mean age: 74±6.2 years for lidocaine group, 74±8.3 years for placebo group; 36 males, 60 female	Daily usage of lidocaine 5% patches for 3 weeks (n = 67) vs. vehicle patches (n = 29)	None post-treatment.	Mean change in Neuropathic Pain Scale (NPS) composite scores from baseline to post-treatment (3 weeks) in lidocaine patch and vehicle patch groups, respectfully: NPS 10 – 15.3, 7.7 (p=0.043), NPS 8 – 14.1, 6.6 (p=0.042), NPS NA – 15.1, 6.8 (p=0.022), NPS 4 – 18.0, 6.6 (p=0.013)	"This study demonstrates that LP reduces the intensity of all common neuropathic pain qualities and thus may be of potential benefit for nonallodynic neuropathic pain states. Furthermore, these findings suggest that peripheral mechanisms may play a role in the pathophysiological development of pain qualities that heretofore have been assumed not to involve peripheral mechanisms, such as "dull," "deep," "sharp," and "burning" pains."	Data suggest lidocaine patch better than placebo in improving all assessed pain qualities for moderate to severe NP patients at 3 weeks.

Rowbotham, 1996 (score=4.0)	Lidocaine Patch	RCT	Sponsored by Harry Hind and NIH Pain Research Training Program Grant NS07265. No mention of COI.	N= 35 patients with post herpetic neuralgia.	Mean age: 75 years; 20 males, 15 females.	Lidocaine patch (n=35) – patients had 420 cm^2 of area with greatest PHN covered by patches containing 5% lidocaine for 12 hrs in two sessions. Vs. Vehicle Patch (n=35) – patients had same surface area covered with patches identical except for the absence of lidocaine. Vs. Observational Patch (n=35) – patients received the same testing procedure and ratings, but no patch was applied.	12 hours.	Lidocaine patch superior to observational at time points 30 mins to 12 hrs (p=0.0001 to p=0.021). Compared to vehicle patch, lidocaine patch application superior at 4, 6, 9, and 12 hrs (p<0.001 to p=0.038). Vehicle patch superior to observational group at 2 and 6 hrs (p=0.016 and p=0.041).	"This study demonstrates that topical 5% lidocaine in patch form is easy to use and relieves post-herpetic neuralgia."	Data suggests 5% lidocaine patches were effective in treating post herpetic neuralgia and were easy to use.

Plasters

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Frerick 2003 (score = 8.0)	Capsaicin, Sports Creams, Wheatgrass Cream	RCT	No mention of sponsorship or COI.	N = 319 with chronic LBP at least 3 months duration	Age range between 19 and 75 years. 137 males, 182 females.	Capsicum plaster 22µg/cm2 1 application a day in morning (n = 159) vs. placebo (n=160) for 3 weeks.	Follow up at 1 and 3 weeks.	Response rates in capsicum group 67% vs. 49% in placebo with minimum 30% reduction in pain. Patients with at least 50% pain reduction: 45.3% capsicum vs. 24.4% placebo. Mean percent reduction of Arhus subscores: current pain score (capsicum 49.4 vs. placebo 36.9, p <0.001), average pain score (38.9 vs. 26.2, p <0.001), worst pain score (36.0 vs. 25.0, p = 0.002), total movement score (20.5 vs. 9.5, p <0.001), disability score (34.8 vs. 23.9, p = 0.001), global Arhus score (33.3 vs. 22.2, p <0.001).	"The lack of systemic side effects and the easy handling of a plaster formulation compared with semi-solid dosage forms (no contact of active drug with the hand, exact quantity of active substance, uniform release, once daily application) support the favourable risk-benefit ration of the capsicum plaster studied."	No systemic adverse events noted. Co-interventions not well described. Capsaicin plaster for 3 weeks in CLBP patients appeared superior to placebo.
Keitel 2001 (score = 6.0)	Capsaicin, Sports Creams,	RCT	No mention of sponsorship or COI.	N = 150 with chronic non-specific back pain at rest	Age range 18-75 years. 78 males, 72 females.	Capsicum pain plaster 11mg (n = 74) vs. placebo (n = 76) for 3 weeks.	Follow up at 12 hours.	Responder rate (pain reduction greater than 30%) significantly better in capsicum group	"As in comparably positive randomized studies with capsaicin cream in	Blinding in question because of sensation and order of active

	Wheatgrass Cream			and during exercise				than placebo (p = 0.0219). Minor adverse effects reported by 15 patients in capsicum group and 9 in placebo group.	patients with osteoarthritis or fibromyalgia it was shown that a capsicum plaster preparation can also be used to advantage in chronic non-specific back pain."	vs. placebo. Co-interventions not well described.
Binder 2009 (score=4.5)	Topical Plasters	RCT	Sponsored by Grünenthal GmbH. Author Binder received honoraria from AUergan, Schwarz, 'Pfizer and Grünenthal. Other authors received financial support from various sources.	N = 263 with post-herpetic neuralgia (PHN) for at least 3 months after rash healing, mean pain intensity score of ≥4 on 11-point numerical ratings scale.	Mean age: 72.5±8.5 years; 112 males, 151 females.	Of the 263 enrolled all underwent an 8-week run-in period to test response to regular plasters. 71 of the responders were chosen for treatment comparison. 5% lidocaine medicated plasters – applied up to 3 for up to 12 hours each day, for up to two weeks, required a plasterfree interval of at least 12 hours (n = 36) vs. Placebo plasters (n = 35)	2 weeks post initial treatment	Kaplan-Meier survival curve for time-to-exit during two week randomized trial (time-to-exit being when a ≥2 point decrease in pain relief measured on 6-point verbal rating scale for two consecutive days, compared to mean pain relief during last week of run-in period): significant difference between 5% lidocaine medicated plaster vs. placebo (p=0.0398)	"This study adds to a growing body of evidence that the 5% lidocaine medicated plaster can be considered a valuable treatment option for patients with PHN, providing beneficial effects on pain, allodynia, quality of life and sleep, with minimal adverse effects."	Data suggest 5% lidocaine plaster may be a beneficial treatment tool for post-herpetic neuralgia.
Baron 2009 (score=4.0)	Topical Plasters	RCT	Sponsored by Grünenthal GmbH. Author Baron received honoraria from Allergan, Schwarz, Pfizer,	N = 229 with post-herpetic neuralgia (PHN) or painful diabetic	Mean age: 61.8±10.2 years; 110 males, 119 females.	4 week mono-therapy of 5% lidocaine plaster or pregabalin, 8 week of combination therapy. 5% lidocaine plaster:	None post-treatment	NRS-3 being average pain intensity over last 3 days measured on 11-point NRS. Changes in NRS-3 score from baseline to	"In patients with PHN and painful DPN failing to respond to monotherapy, combination therapy with 5%	Open label trial. Data suggest 5% lidocaine plaster had comparable efficacy to pregabalin in DPN but showed

			Grünenthal, Medtronic, Mundipharma, Eisai, Sanofi-Pfizer, and Genzyme and research funding from Pfizer, Grünenthal, and Genzyme.	polyneuropathy (DPN)		three to four plasters for up to 12 hours during each 24-hour period. Pregabalin: 150 mg/day first week, 300 mg/day second week, those with insufficient analgesic efficacy, defined (average pain intensity of ≥4) 600 mg/day. Comparative treatment, combination treatment: (L) 5% lidocaine medicated plaster, 5% lidocaine medicated plaster (n = 71) vs. (P) Pregabalin, pregabalin (n = 57) vs. (LP) 5% lidocaine medicated plaster, pregabalin (n = 57) vs. (PL) Pregabalin, 5% lidocaine medicated plaster (n = 44)		combination phase: L -0.7±1.2, P -0.6±1.3, LP -2.5±1.6, PL -1.7±1.8 (no p-values reported)	lidocaine medicated plaster and pregabalin provides additional clinically relevant pain relief and is safe and well-tolerated."	better efficacy for PHN patients.

Pumps/Sprays

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kanai 2009 (score=5.0)	Pumps/Sprays	RCT	No mention of sponsorship or COI.	N = 24 with post-herpetic neuralgia	Mean age: 71 for XPS group, 70 for saline group; 13 males, 11 females.	Metered-dose pump of 8% lidocaine (Xylocaine [XPS]), maximum dose of 30 sprayes (0.1 mL/single spray, 30 times), for 7 days (n = 12) vs. Saline pump solution for same duration (n = 12). Crossover study design so both groups received both treatments.	None.	Changes in visual analog scale scores for persistent pain at baseline and after 15 minutes of pump administration, respectfully: Period 1: XPS/saline group – 6.2±1.3, 2.2±2.4 ($p < 0.01$ comapred to basline, $p < 0.01$ compared to saline/XPS group). Saline/XPS group – 6.0±2.1, 5.4±1.6 ($p < 0.05$). Period 2: XPS/saline group – 6.2±1.3, 6.0±1.6. Saline/XPS group – 6.0±2.1, 2.4±2.6 ($p < 0.01$ compared to baseline, $p < 0.001$ compared to XPS/saline group)	"In both studies, XPS provided a significant improvement in PHN due to its prompt analgesia, lack of systemic side effects, and convenience of use."	Crossover study. Data suggest XPS improves PHN associated pain.
Agrawal 2007 (score=5.0)	Glyceryl trinitrate spray	RCT	No mention of COI or sponsorship.	N = 43 diabetic for ≥ 6 months on stable dose of insulin or oral	Mean age: Group A 57.51±4.96 years, Group B	Randomized trial containing two week wash out period. All participants	None post treatment	Changes in pain on VAS for group A GTN spray and group B placebo, respectfully: Week 0	"GTN spray, a well tolerated drug, provides significant improvement in	Crossover design. Data suggest efficacy.

				hypoglycemic agents, HbA1c < 11	58.62±6.09 years; No gender distribution described.	received 4 weeks of both treatments. Started with glyceryl trinitrate (GTN) spray, spray on both feed with one actuation each (0.4 mg/actuation) before sleeping (n = 22) vs. Started with placebo (n = 21)		7.18±0.73 vs. 7.57±0.81 (p=0.105), Week 4 4.68±1.36 vs. 6.90±1.09 (p<0.001). Changes in pain on VAS for group A placebo and group B GTN spray, respectfully: Week 6 7.05±1.09 vs. 7.52±0.60 (p=0.084), Week 10 6.45±1.34 vs. 4.57±0.98 (p<0.001)	painful diabetic neuropathy. These data provide a basis for future trials for longer duration in a larger group of patients."	

TENS

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Oosterhof 2006 (score = 8.5)	Mixed Chronic Pain Disorders	RCT	Funded by The Netherlands Organization for Health Research and Development Grant 940-31-053. No mention of COI.	N = 163 with chronic pain and mixture of disorders including peripheral neuropathy, OA, osteoporosis, bursitis, tendinitis, or bone, soft tissue, or visceral pain	Mean age is 50.2 years. 66 males, 97 females.	TENS, high frequency (n = 81) vs. sham TENS (n = 82) for 10 days.	2 week follow up.	Results suggest a significant psychological aspect to response rates, with improvements just in those satisfied with treatment, regardless of whether it was active or placebo. No significant differences between groups.	"The proportions of patients satisfied with treatment result differed significantly for TENS compared to sham TENS. There were no differences in pain intensity found for patients treated with TENS or sham TENS. Only for patients satisfied with treatment results pain [did] intensity gradually decrease equally both for TENS and sham TENS with repeated treatment application."	Second report noted better results for bone and soft tissue vs. OA, spine or neuropathic pain.

Xǔ 2014 (7.5)	TENS	RCT	No mention of sponsorship or COI.	N = 90 patients with postherpetic neuralgia.	Mean age: 69.5 years; 45 males, 45 females.	T-MB group (n=30) – TENS and local injections of cobalamin. Vs. T-LD group (n=30) – TENS and local injections of Lidocaine. Vs. T-BL group (n=30) – TENS and a combination of cobalamin and lidocaine.	8 weeks.	The comparison of the EQ-VAS scores before and after treatment at baseline mean reported T-MD (26.07), T-LD (25.83), and T-BL (27.50). p=0.887. The endpoint mean reports T-MB (63.67), T-LD (38.00), and T-BL (63.53). p<0.001. At endpoint, the comparisons between the groups reporting difference (95% CI) and p-values are: T-MB vs T-LD: 25.67, P<0.001; T-MB vs. T-BL: 0.13, p=0.969; T-BL vs. T-LD: 25.53, p<0.001.	"TENS in combination with local cobalamin injection has a significant analgesic effect."	Data suggests TENS plus injections of Cobalamin provides substantial analgesic effects for PHN.
Langley 1984 (score = 7.5)	TENS	RCT	Sponsored by the Arthritis and Rheumatism Foundation of New Zealand. No mention of COI.	N = 33 with RA	Mean age is 54 years. 9 males, 24 females.	High-frequency TENS (20 minutes), frequency 100Hz (n = 11) vs. 20 minutes of acupuncture-like TENS, frequency 2Hz (n = 11) vs. placebo TENS (n = 11).	24 hour follow up.	Acupuncture-like TENS group had higher total joint tenderness scores. No significant difference between groups at any post-treatment assessments for resting pain and grip pain. NS between groups for total joint tenderness scores.	"[T]ENS given at high intensity is no better than placebo applied with strong suggestion. This does not preclude the use of TENS to relieve pain and tenderness in patients with rheumatoid arthritis as it is effective, non-invasive and free of side effects."	Study suggests TENS not effective for rheumatoid arthritis. However, this is a short term experimental study.

Hsueh 1997 (score = 6.0)	TENS	RCT	No mention of COI or sponsorship.	N = 60 with unilateral upper trapezius myofascial trigger points	Mean age: 41.1 years for group A, 42.7 years for group B, 44.4 years for group C; 25 males; 35 females.	Sham electrotherapy controls (Group A, n = 18) vs. electrical nerve stimulation with frequency of 60 Hz (ENS, Group B, n = 20) vs. electrical muscle simulation frequency of 10 Hz (EMS, Group C, n = 22) for 20 minutes	None.	Pain intensity: Group A 6.1±9.8 vs. Group B 57.8±24.8 vs. Group C 15.8±34.1, p <0.05. Pain threshold: Group A 1.9±23.3 vs. Group B 45.9±37.4 vs. Group C 13.6±32.3, p <0.05. ROM: Group A 7.4±13.2 vs. Group B 15.2±23.5 vs. Group C 82.73±75.7, p <0.05.	"It is concluded that ENS is more effective for immediate relief of myofascial trigger point pain than EMS, and EMS has a better effect on immediate release of muscle tightness than ENS."	Study is short-term trial of 1 20-minute treatment, thus strong conclusions about efficacy appear unwarranted
Koke 2004 (score = 6.0)	TENS	RCT/Cross over trial	No mention of sponsorship or COI.	N = 180 with chronic pain including LBP (20-22% each arm), neuropathic (12-15%), cervical spinal (10-13%), "chronic pain syndrome" (10-14%), CRPS-II (5-13%)	Mean age is 50.3 years. 65 males, 115 females.	High-frequency TENS (80Hz, pulse duration 80µs) vs. high-frequency, high-intensity TENS (9Hz, 250µs) vs. control TENS (30Hz, 250µs). TENS 4-6 times a day for 1-hour periods at sensory threshold intensity for 2 weeks with 2 week washout period between treatments.	Follow up at 6 months.	Fifty-six percent reported TENS useful and continued to use it after trial. Authors found no differences in effectiveness for 3 types of TENS.	"[T]here were no differences in effectiveness for the three types of TENS used in this study. Because no placebo group was included, no definite conclusions on effectiveness of TENS in general in the treatment of chronic pain could be made."	As no true placebo group, utility of TENS cannot be addressed.
Gossrau 2011 (5.0)	TENS	RCT	No COI and no mention of sponsorship.	N=41 patients with painful diabetic neuropathy	Mean age: 65.35 years; no	Verum group (n=21): received micro-TENS therapy vs	1 month	Post treatment for verum group NPS score was 36.23±15 and for the placebo	"The pain reduction with the applied transcutaneous electrotherapy regimen	Data suggests (in) efficacy placebo effect.

					mention of sex.	Placebo group (n=19): received with a placebo therapy		group NPS was 32.74±17.2 (p>0.18). Six of 21 patients in verum group showed reduction of 30% at least in NPS score between T1 and T2 (p>0.09). PDI scores for verum group at T1 were 22.05±16.5 and at T2 were 17.7±15.5. PDI scores for placebo group at T1 were 21.79±15 and at T2 were 18±14.6 (p<0.8).	is not superior to a placebo treatment."	
Chee 1986 (score = 5.0)	TENS	RCT	No mention of sponsorship or COI.	N = 25 chiropractic school volunteer students with neck and shoulder pain	Mean age is 44.4 years. 25 males, 35 females.	TENS (Electro-Acuscope 80) vs. placebo (groups equal) 6 sessions over 2 weeks treatment for trigger points.	Follow up at 2 months.	Significant improvement in trigger point pain from 1st and 5th session in TENS group (p = 0.001).	"[M]icroamperage stimulation is effective in the treatment of trigger points."	Details and outcomes sparse. Chiropractic students a select group that is difficult to generalize beliefs and education.
Kumar 1998 (4.5)	TENS	RCT	No mention of sponsorship or COI.	N=26 patients with peripheral neuropathy	Mean age: 58.6 years; 10 males, 13 females	All patients were prescribed 50 mg amitriptyline and revaluated after 4 weeks into randomized groups. Sham therapy (n=9): received machines that had inactive	16 weeks	Fifteen of 26 patients observed symptomatic relief after 4 weeks of therapy while 8 patients had no relief. Pain scores reduced from 3.8±0.1 to 2.9±0.2 (p<0.01). For sham treatment pain	"Our clinical observations suggest that transeutaneous electrotherapy is effective in reducing the pain associated with peripheral neuropathy. This form of therapy may	Data suggest electrotherapy may help manage pain from peripheral neuropathy.

						output terminals vs Electrotherapy group (n=14): received electrotherapy machines for 12 weeks		socres declined from 2.8±0.3 to 1.9±0.5 (p<.03). For electrotherapy group pain score declined from 3.2±0.2 to 1.4±0.4 (p<.01).	he a useful adjunctive modality when it is combined with a pharmacological agent, such as amitriptyline, to augment symptomatic relief."	
Ing 2015 (4.0)	TENS	RCT	Sponsored by grants from the National Institute on Minority Health and Health Disparities H54MD007584 and G12MD007601 from the National Institutes of Health and no COI.	N=20 patients with chronic post-herpetic neuralgia	Mean age: 71.7 years; 8 males, 12 females	Electronic biofeedback treatment (n=10): received 3 consecutive sessions for 15 minutes at 3-7 day intervals up to 6 sessions vs Sham control (n=10): received same sessions with sham device that emits electrical stimulation of 3 mA	Following every 2 treatment sessions.	Average reduction of NPSS score for second visit was -18.4% for treatment compared to sham with 1.3% and baseline to third NPSS a reduction of 29.8% for TBM and 12.2% for sham device. TBM group showed overall NPSS decrease of 38.9% (p<.01). Patients allowed to switch to TBM and initial TBM patients observed average of 39.9% reduction (p<.0001).	"Further investigation of this Food and Drug Administration, class 2 accepted, electronic device for relief of pain is warranted for patients with a history of recalcitrant postherpetic neuralgia."	Pilot study suggesting efficacy with TENS vs SHAM for reduction in PHN pain.

rTMS

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hosomi 2013 (7.5)	rTMS	RCT	No COI and sponsored by the Japanese Ministry of Health, Labour and Welfare with a Health and Labour Sciences Research Grant. This research was partly supported by Japanese MEXT SRPBS.	N=64 patients with neuropathic pain	Mean age: 60.6 years; 40 males, 24 females	Group A (n=29): 10 daily 5-Hz rTMS (500 pulses/sessions) of primary motor cortex vs Group B (n=35): sham stimulation	17 days	Group A showed more reductions of VAS than Group B. ANOVA measures for intervention ($p<0.001$) and time ($p<0.001$), day ($p=0.325$), and period ($p=0.464$). Mean VAS reduction rates (10 sessions) for real rTMS and sham were 13.31% (8.24-18.39) vs 7.49% (3.45– 11.53) just after stimulation, and 5.11% (0.05–10.18) vs -3.62% (9.27–2.03) 60 min after stimulation.	"Our findings demonstrate that daily high-frequency rTMS of M1 is tolerable and transiently provides modest pain relief in NP patients."	Crossover study, SHAM controlled. Data suggests only modest short term efficacy with rTMS for improved VAS and SF-MPQ score but no significant long term benefits.
Yilmaz 2014 (5.5)	rTMS	RCT	No mention of sponsorship or COI.	N=17 patients with spinal cord injury and chronic neuropathic pain.	Mean age: 38.41 years; 17 males, 0 females.	Real rTMS group (n=9) – patients received one treatment session for 10 weeks. 30 trains of 10-Hz stimuli for a duration of 5 seconds at an inter-train	Baseline, 10 days, 6 weeks, 6 months.	The VAS scores for the Real rTMS group and the Sham rTMS group were 7.0, 7.0, $p>0.05$ at baseline; 5.0, 6.0, $p>0.05$ at 10 days; 5.0, 7.0 $p>0.05$ at 6 weeks; 7.0, 7.0, $p>0.05$, respectively.	"Our results demonstrated analgesic effect of rTMS on intractable neuropathic pain in SCI was not superior to placebo. However, middle-term (over	Small sample. Data suggests lack of efficacy.

						interval of 25 seconds, a total of 1500 pulses, was applied. The coil was angled towards the head. Vs. Sham rTMS group (n=7) – patients received the same protocol but the coil was angled away from the head.			6 weeks) pain relief by rTMS is encouraging and suggests the need for future studies with a larger sample size."	
Slotty 2015 (5.5)	rTMS	RCT	No sponsorship or COI.	N = 7 patients already successfully treated with MCS for neuropathic pain.	Mean age: 65.4 years; 2 males, 5 females.	Baseline PMT (n=) – "medium" setting stimulation Vs. 10% higher PMT (n=) – "high" setting, 10% higher than baseline. Vs. 10% lower (n=) – "low" setting, 10% lower than baseline.	No follow up.	The best treatment response (mean VAS 3.4) was seen with the medium setting which was at a mean of 62% PMT. High and low settings both resulted in a significant increase in pain compared with the medium setting (mean VAS 6.0 and 6.3, respectively) and a significant decrease in SF-36 scores. No significant difference in pain control was observed between the high and low settings. The mean	"We propose that the PMT represents an important parameter that measures the degree to which MCS may be affecting the motor cortex. A mean PMT of 62% was required for effective pain relief. Higher settings did not result in increased therapeutic efficacy but rather in a significant increase in pain. Targeting therapy to a PMT level may	Small sample. Data suggests MCS "may" affect the motor cortex.

								time from changes in treatment settings to reported change in pain level was 2.9 days (±1.0 day).	speed initial programming, allow more consistent longitudinal follow-up, and be a basis for a standardized programming paradigm."	
André-Obadia 2014 (4.5)	rTMS	RCT	No sponsor and no COI.	N=20 patients with chronic pharmaco-resistant neuropathic pain.	Mean age: 54.3±9.7 years; 11 males, 9 females	Active treatment (n=): received 20 consecutive trains of 80 simulations of 20 Hz-rTMS vs Sham treatment (n=): received placebo rTMS using a sham coil at identical frequency	Mean follow-up 6.1±2.6 years	NRS scores after active rTMS was 4.0 p<.01 or 14.6% relief compared to sham of 2.9%. CPa scores after active rTMS and long-term MCS (p=.02) had 90% positive predictive value and 67% negative predictive value.	"Half of the patients still retain a significant benefit after 2 – 9 years of continuous MCS, and this can be reasonably predicted by preoperative rTMS. Adding drug intake and QoL estimates to raw pain scores allows a more realistic assessment of long-term benefits and enhance the rTMS predictive value."	Crossover design. Small sample, sparse methods.
Saitoh 2007 (4.0)	rTMS	RCT	No mention of sponsorship or COI.	N = 13 patients with intractable deafferentation pain.	Mean age: 59.4 years; 7 males, 6 females.	All 13 patients underwent sham stimulation and	Baseline and 15 minute intervals	The reduction rate of VAS at 5-Hz and 10-Hz rTMS at 0 min were 4.9 (p<0.05) and 4.5 (p<0.05),	"High-frequency (5- or 10-Hz) rTMS of the precentral gyrus can reduce intractable	Non-randomized, small sample. Data suggest high frequency

						1-, 5-, and 10-Hz rTMS of the precentral gyrus. The rTMS was applied through a figure-eight coil, which provides limited cortical stimulation.	until 180 minutes.	respectively. At 15 mins: 3.1 ($p<0.05$) and 3.5 ($p<0.05$). At 30 mins: 2.8 ($p<0.05$) and 3.3 ($p<0.05$). At 60 mins: 2.3 ($p<0.05$) and 2.6 ($p<0.05$). At 90 mins: 1.5 ($p<0.05$) and 1.8 ($p<0.05$). At 180 mins: 1.1 ($p<0.05$) and 1.1 ($p<0.05$). Values are listed respective to 5-Hz and 10 Hz.	deafferentation pain, but low-frequency stimulation (at 1 Hz) cannot. Patients with a noncerebral lesion are more suitable candidates for high-frequency rTMS of the precentral gyrus."	rTMS can decrease deafferentation pain and it appears patients with noncerebral lesions respond best.

tDCS

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Portilla 2013 (4.5)	tDCS	RCT	Supported by department funds. No COI.	N=3 patients with chronic neuropathic pain following brain injury.	Mean age: 42.3 years; 1 male, 2 females.	Active tDCS (n=3) – During active tDCS, a constant current of 2 mA was delivered for 20 minutes. Vs. Sham (n=3) - During the sham condition, the same electrode montage was used; however, current was	1 week washout period.	Changes in cortical excitability before tDCS and after tDCS in the active tDCS group for Mean MEP (mV) were 1.32 and 1.17 and for Mean absolute CSP (sec) were 0.07 and 0.09, respectively. In the Sham stimulation the changes in cortical excitability for Mean MEP (mV) were 1.54 and 1.55 and for Mean absolute CSP	"This case series shows early evidence that chronic pain following burn injury may share similar central neural mechanisms, which could be modulated using tDCS."	Crossover design. Descriptive study. Sample too small to make conclusions.

						applied only for the initial 30 seconds and then automatically turned off.		(sec) were 0.12 and 0.09, respective to before and after tDCS.		

Pulsed Radiofrequency

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ke 2013 (6.5)	Pulsed Radiofrequency	RCT	No COI or Sponsorship.	N=96 patients with thoracic PHN.	Mean age: 72.16 years; 47 males, 49 females	PRF group (n=48): received pulsed radiofrequency vs Sham group (n=48): did not receive radiofrequency energy	1, 2, 3, 6 months	For PRF group VAS decreased by .221 points (-.23- -0.18; t=-15.72, p<0.0001). compared to the sham group. Interaction between treatment and follow-up time (F=29.07, p<0.001). Tramadol use was low in PRF group than sham with a decrease of 56.38 points (42.26-69.93; t=7.09, p<0.001). Improvement in SF-36 score improvement after treatment compared to sham was p<0.05~0.01).	"The strategy that the angulus costae be used as the PRF puncture point of an electrode needle and the final localization of the needle tip as determined by sensory testing is an effective and safe therapeutic alternative for thoracic PHN treatment. Benefits include that the procedure is minimally invasive, provides short-term pain relief, and improves quality of life."	Medication use pre-procedure not described. Data suggests short term pain relief with PRF for thoracic PHN treatment as rescue medication use and VAS decreased in treatment group.

Cranial Electrotherapy Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Tan 2011 (5.5)	Cranial Electrotherapy Stimulation	RCT	Sponsored by the Veterans Affairs Rehabilitation Research and Development Service. Electromedical Products International, Inc., Mineral Wells, Texas, provided the active and sham CES devices and the necessary batteries, ear clip pads, and wetting solution. No COI.	N=105 patients with spinal cord injury and chronic neuropathic pain.	Mean age: 52.3 years; 90 males, 15 males.	Active CES (n=46) – participant were given a device to record neuropathic pain before and after each treatment session. Persons in the treatment group received 1 hour per day of 100 µA sub-sensation active CES. Vs. Sham CES (N=59) – Participants given device to record neuropathic pain before and after treatment. received 1 hour per day of sham CES.	3 weeks.	In the blinded phase, the BPI pain interference subscale reports 56.2 pre ($p \leq 0.001$) and 39.5 post ($p \leq 0.001$) in the active group and 38.5 pre ($p \leq 0.001$) and 32.2 post ($p \leq 0.01$) in the Sham group. In the open-label phase, BPI pain intensity subscale reports 21.8 pre ($p \leq 0.05$) and 2.08 post ($p \leq 0.05$) in the sham group.	"On average, CES appears to have provided a small but statistically significant improvement in pain intensity and pain interference with few troublesome side effects. Individual results varied from no pain relief to a great deal of relief."	Data suggest cranial electrotherapy stimulation improved both pain intensity and pain interference.

Raphael 2011 (5.5)	Cranial Electrotherapy Stimulation	RCT	Sponsored by Higher Education Funding Council for England and Algotec Ltd. No mention of COI.	N=31 patients with chronic pain with surface hyperalgesia	Mean age: 55.8±15.5 years; 13 males, 18 females	Active Treatment (N=unknown) received PENS between 2-100 Hz every 3 seconds for 25 minutes vs Control Treatment (n=unknown) received simulation electrical stimulation for 25 minutes	None	For active treatment, median NRS score for pain varies from 7.5±1 before therapy to 0.5 after therapy (Z=-4.206, P<0.0005). Mean PPT changed from 202 gm±137 gm before therapy to 626 gm±228gm (Z=-4.373, p<0.0005). For control treatment, median NRS scores was 7.5±1 before and after therapy (Z=-1, P=0.317). Mean PPT changed from 202±134gm before therapy to 206±133 gm after therapy (Z=-1.915, P=0.055).	"PENS therapy appears to be effective in providing short-term pain relief in chronic pain conditions. Studies, involving larger sample sizes and longer follow-up are recommended."	Crossover trial. Small sample. PENS may have short term benefit in chronic pain patients.

FREMS

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Bosi 2005 (score=5.0)	FREMS	RCT	Supported in part by a research grant from Lorenz Biotech (Medolla, Italy). No COI.	N = 31 patients with painful neuropathy	Mean age: 61.5 years; gender: not specified	Each patient (n=31) with painful neuropathy associated with decreased nerve conduction	4 month follow up	FREMS induced a significant reduction in daytime and night-time VAS pain score (all p<0.02). Furthermore, FREMS induced a significant increase	"FREMS is a safe and effective therapy for neuropathic pain in patients with diabetes and is able to modify some parameters	Crossover study. Data suggest significant reduction in both day and night VAS scores from FREMS and benefits were

						velocity (<40 m/s) and increased vibration perception threshold (>25 V) received two series of ten treatments of either frequency-modulated electromagnetic neural stimulation (FREMS) or placebo in random sequence, with each series lasting no more than 3 weeks.		in sensory tactile perception, as assessed by monofilament; a decrease in foot vibration perception threshold, as measured by a biothesiometer; and an increase in motor nerve conduction velocity (all p<0.01). No significant changes were observed after placebo. Comparison of measurements at the 4-month follow-up with those at baseline revealed that a significant benefit persisted for all measures that showed an improvement at the end of treatment, with an additional improvement in quality of life evaluated by the Short Form-36 questionnaire (all p< 0.05). No significant side effects were recorded during the study.	of peripheral nerve function."	maintained for 4 months.
Bosi 2013 (score=5.0)	FREMS	RCT	Supported in part by a research grant from Lorenz	N = 31 patients with	Mean age: 61.5 years;	Each patient (n=31) with	None	Adjusted mean change in motor nerve conduction	"FREMS proved to be a safe treatment for	Data suggest FREMS provides immediate but

			Biotech (Medolla, Italy). No COI.	painful neuropathy	gender: not specified	painful neuropathy associated with decreased nerve conduction velocity (<40 m/s) and increased vibration perception threshold (>25 V) received two series of ten treatments of either frequency-modulated electromagnetic neural stimulation (FREMS) or placebo in random sequence, with each series lasting no more than 3 weeks.		velocity (NCV) from baseline to 4 month follow up for FREMS and placebo groups, respectfully: Intention-to-treat population – Deep peroneal nerve: 0.74±0.71, 0.06±1.38 (p>0.05), Tibial nerve: 2.08±0.84, 0.61±0.43 (p>0.05), Sural nerve: 0.80±1.08, -0.91±1.13 (p>0.05). Per protocol population - Deep peroneal nerve: 0.98±0.72, -0.05±0.44 (p=0.049), Tibial nerve: 0.76±0.59, 0.58±0.46 (p>0.05), Sural nerve: 1.13±0.87, 0.44±0.96 (p>0.05)	symptomatic diabetic neuropathy, with immediate, although transient, reduction in pain, and no effect on NCV."	transient relief of diabetic associated neuropathic pain.

Irradiation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Nawfar 2011 (score=5.0)	Monochromatic infrared energy therapy treatment	RCT	Sponsored by a short term grant provided by Universiti Sains Malaysia. No mention of COI.	N = 24 (30 feet) patients with diabetic neuropathy.	Mean age is 54.4 years. 8 male, 16 females.	Sham group (N=15 feet) vs. Monochromatic infrared energy therapy treatment group (N=15 feet)	Follow up at 6 weeks and 3 months.	No significant difference was found between neuropathic foot of diabetic patients in both MIRE and sham groups.	"No improvement of neuropathy was observed following MIRE treatment in the neuropathic feet of diabetic patients."	Data suggest lack of efficacy.
Valtonen, 1975 (score=5.0)	Roentgen Irradiation	RCT	No mention of COI or sponsorship.	N=104 patients with painful disorders of joints and muscles	Mean age: 58.5 years; 32 males, 72 females	Roentgen therapy group (n=51): vs Placebo group (n=53):	2, 6 weeks	Fifty-nine percent of patients in roentgen group and 65% of placebo group were improved. Placebo group showed better improvement.	"(i)t seems obvious that roentgen radiation therapy of painful degenerative and inflammatory musculoskeletal conditions has only the effect of a powerful placebo. Its use in the treatment of painful conditions should therefore be abandoned."	Data suggest each of efficacy with a slight trend towards placebo group.

External Irradiation for Sympathectomy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size/Population:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Basford 2003 (score = 6.5)	External Irradiation	RCT/Cross over Trial	Funded by Tokyo Co., Ltd., 1131-1 Higashi-Naganuma, Inagi-City, Tokyo 206-0802, Japan. No mention of COI.	N = 18 with unilateral upper extremity CRPS I	Mean age is 40 years. 3 males, 15 females.	Transcutaneous irradiation of right stellate ganglion with linearly polarized 0.6-1.6µm light vs. no medication or other exposures (Phase I, n = 6 with normal neurological exams). Phase II: double-blinded evaluation of active and placebo radiation (n=12) (6 upper extremity CRPS I/6 "normal" controls). Skin temperature, heart rate, sudomotor function, vasomotor tone monitored before, during, 30 min. following irradiation. Analgesic and sensory effects assessed over same period and 1 and 2 weeks later.	2 week follow up.	Pain not statistically significantly reduced. Authors noted that 3 of 6 CRPS I subjects, but no control subjects, experienced sensation of warmth following active irradiation, and 2 CRPS I subjects reported more than 50% pain reduction.	"However, four noted minimal or no change and improvement did not reach statistical significance for the group as a whole. No statistically significant changes in autonomic function were noted."	No adverse consequences observed. Study found preliminary evidence that external radiation for purposes of producing a permanent sympathetic block is technically possible. Likely underpowered to detect pain reduction. However, it does not show evidence of efficacy of intervention, especially long-term improvements.

Diathermy

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Sweetman 1993 (score = 6.0)	Diathermy	RCT	Funded by the Arthritis and Rheumatism Council. No mention of COI.	N = 400 with chronic, subacute, or acute LBP	Mean age is 41.0 years; 200 males, 200 females.	Compared 100 subjects each with extension exercises, diathermy, and traction and controls on sham diathermy among 400 patients. Treatments 20 minutes, 3 times a week for 2 weeks.	Follow up at 2 weeks.	No treatment superior to another.	"Seven distinct patterns of low back pain emerged after the data of 301 patients from the therapeutic trial was analyzed for classification. Multivariate significance level (p=0.02) was obtained when nine treatment outcome measures that were used to examine the interaction among four treatment groups and seven different patterns of back pain. Thus, the hypothesis was established indicating that treatment effects summarized the different responses based on the diagnosis."	While randomized, study may have been biased against diathermy and control groups based on worsening back pain in past month.

Magnets and Magnetic Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size/Population:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Collacott 2000 (score = 7.5)	Magnets and Magnetic Stimulation	Crossover Trial	No mention of sponsorship or COI.	N = 20 with low back pain for at least 6 months with no new neurological deficits	Mean age is 60 years. 19 males, 1 female.	Magnets vs. sham magnets each for 1 week before crossing over with a 1 week washout period between trials. Each group applied devices 6 hours a day 3 days a week for total 18 hours of treatment.	Follow up at 2 weeks.	No significant differences between groups.	"Application of 1 variety of permanent magnet had no effect on our small group of subjects with chronic low back pain.	This is a pilot study.
Durmus 2004 (score = 6.0)	Magnets and Magnetic Stimulation	RCT	No mention of sponsorship or COI.	N = 40 with CRPS Type I subsequent to trauma (Colles fracture)	Mean age is 39.1 years; 21 males, 19 females.	Compared electromagnetic field treatment administered with calcitonin and exercise. All patients pre-treated with calcitonin (100 units) and half (Group 1, n = 20) received electromagnetic field treatment 5 times a week for 6 weeks, and other half (Group 2, n = 20) received placebo treatment by being placed in same device without it being switched on (60 minutes a session).	Follow up at 3, 6, and 8 weeks.	VAS-activity: EFT (4.25±2.10) vs. placebo (3.00±2.20), p= 0.033. NS between groups for all other outcomes.	"The absence of a significant difference between the two groups in the assessment parameters has been interpreted as evidence that electromagnetic field treatment does not provide additional benefit to calcitonin and exercise treatment."	Blinding measures not well described. Baseline differences in pain scales not significant, but treatment group has higher baseline pain values than controls, and post-treatment those differences disappeared, so suggestion that reduction in pain ratings is significant may be misleading.

Low-level Laser Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size/Population:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Waylonis 1988 (score = 4.5)	Low-level Laser Therapy	RCT	Funded by a grant from the Central Ohio Fibrositis Association. No COI.	N = 55 with myofascial pain	Age greater than 18; 6 males, 56 females of 62 originally screened.	Group 1 received placebo laser therapy for 1st and 2nd series of treatments. Groups 2 and 3 received 1 series of laser therapy and 1 placebo therapy, differing in order in which treatments administered. Group 4 received laser therapy for 1st and 2nd series; 2 sessions of 5 treatments given 6 weeks apart.	Follow up of 6 weeks.	No significant difference between treatment groups.	"Specifically, no difference in pain response and treatment effectiveness was noted in the treated and placebo groups." The authors found that "low-power laser therapy applied to acupuncture points did not duplicate the results previously described using acupuncture on patients with fibromyalgia."	Few data provided. Mixture of diagnostic terms leaves it unclear whether patients had limited or widespread tender/trigger points, but appears more likely to have been fibromyalgia.

Botulinum Toxin A

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ranoux 2008 (7.5)	Botulinum Toxin A	RCT	Sponsored by Institut National de la Sante´ et de la Recherche Me´dicale. No mention of COI.	N=29 patients with neuropathic pain.	Mean age: 51.8 years; 10 males, 19 females.	BTX-A (n=15) – Patients received a one-time intradermal injection of 100U/vial BTX-A. Vs. Placebo (n=14) – patients received a one-time intradermal injection of the placebo, consisting of an equal volume of saline (9% NaCl).	Baseline, 4, 12, and 24 weeks.	The mean pain (VAS) scores the BTX-A and placebo at baseline, week 4, week 12, and week 24 are: 68.6 and 60.0; 45.0 ($p<0.05$) and 54.0; 40.3 ($p<0.05$) and 56.4; 47.9 ($p<0.05$) and 58.5; respectively.	"We conclude that intradermal injection of BTX-A has direct analgesic effects in patients with focal chronic neuropathic pain associated with allodynia. It is suggested that the observed analgesia may be caused by a local peripheral effect of BTX-A on nociceptive fibers, although subsequent central effects are possible. The treatment was particularly well tolerated. These data suggest that BTX-A should be considered as part of the therapeutic arsenal against focal neuropathic states."	Intradermal injection. Single injection treatment but each patient received 40 prickles. Data suggest BTX-A has direct analgesic benefits in chronic NP pain patients.
Apalla 2013 (7.5)	Botulinum Toxin A	RCT	No mention of sponsorship. No COI.	N=30 patients with postherpetic neuralgia.	Mean age: 75.35 years; 18 males, 12 females.	Botox (n=15) – patients received 40 injections of 100 IU BTX-A, injected subcutaneously in chessboard manner. Vs.	Every 2 weeks for 12 weeks and every 4 weeks, until week 24.	50% reduction in VAS pain score for 13 patients in BTX-A group, compared with none of the placebo patients (NNT=1.2, 95% CI, 2-1; ARR=0.87, 95% CI, 055-096; P<0.001).	"In summary, our results demonstrate that in terms of efficacy, safety, and tolerability, BTX-A is a very promising therapeutic modality for PHN, and could be a welcome addition to the armamentarium of agents used to treat herpes-associated pain. Further	Single dose trial. Data suggest BTX-A improves pain and sleep quality in PHN patients.

						Placebo (n=15) – Placebo group received normal saline, dispensed exactly the same way.			studies are warranted to optimize and establish treatment protocols for long-term pain management ”	
Xiao 2010 (5.5)	Botulinum Toxin A	RCT	Sponsored by the Guangdong Healthcare Department. No mention of COI.	N=60 patients with postherpetic neuralgia.	Mean age: 67.3 years; 28 males, 32 females.	BTX-A (n=20) – patients received 5 u/mL injections of BTX-A at baseline. Vs. Lidocaine (n=20) – patients received 5 u/mL injections of lidocaine at baseline. Vs. Placebo (n=20) - patients received 5 u/mL injections of saline at baseline.	3 months.	BTX-A, Lidocaine, and placebo groups reported the following VAS scores at baseline, day 1, day 7, and the 3 month follow up: 7.7, 8.0, 8.0; 6.5, 5.0 ($p<0.01$ compared to BTA-X and baseline), 6.9; 3.0 ($p<0.01$ compared to pretreatment), 5.3 ($p<0.01$ compared to pretreatment and BTX-A), 5.0 ($p<0.01$ compared to pretreatment and BTX-A); 3.8 ($p<0.01$ compared to pretreatment and BTX-A), 5.0 ($p<0.01$ compared to pretreatment and BTX-A), 5.7 ($p<0.01$ compared to pretreatment and BTX-A); respectively.	“Subcutaneous administration of BTX-A significantly decreased pain in PHN and reduced opioid use compared with lidocaine and placebo at day 7 and 3 months’ post-treatment. It also increased subjects’ sleep times.”	Single injection treatment. Data suggests all 3 groups improved with BTX-A showing most improved pain scores.

Gangliosides (Cronossial)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Staughton 1990 (5.0)	Gangliosides (Cronossial)	RCT	No mention of sponsorship or COI.	N=25 patients with postherpetic neuralgia.	Mean age: 68.8 years; 11 males, 14 females.	Cronassial (n=12) – patients received 11 subcutanous injections over a period of 27 days of 100 mg in 2 mL buffered solution. Vs. Placebo (n=13) – patients received the same, but with the placebo.	No follow up.	Improvement in sleep pattern score for 'Cronassial' group at 4 weeks ($p<0.01$) and week 8 ($p<0.02$). change from baseline is great in Cronassial than placebo at week 4 ($p<0.005$) and week 8 ($p<0.02$). Reduction in hyperaesthesia from baseline in mean pain level at 2, 4, and 8 weeks ($p<0.005$).	"In conclusion, this study has shown that a course of treatment with subcutaneous 'Cronassial' is well tolerated in patients with post-herpetic neuralgia."	Small sample. Data suggest improved sleep and hyperaesthesia with cronassial.

Lidocaine

Viola 2006 (score = 8.5)	Lidocaine	Crossover Trial	Sponsored by NovoNordisk, No mention of COI.	N = 15 with diabetic peripheral neuropathy	Mean age is 64.3 years. 7 males, 8 females.	Weekly treatments lasting 4 hours each for 4 weeks saline (p) vs. 500mg/500mL (L) vs. 750mg/500 mL (H) intravenous lignocaine. All patients received all 3 study doses in random order. Follow-up weekly until 28 days.	Follow up at 2 and 4 weeks.	Both lignocaine treatments favored for Pain Rating Index (PRI) and Present Pain Intensity (PPI) ($p<0.05$).	"[I]ntravenous lignocaine administered over 4 h in a dose of 5 to 7.5 mg/kg provides relief from intractable diabetic peripheral neuropathic pain for up to 28 days."	Short-term follow-up after each injection. Data suggest modest pain improvements. Functional benefit unclear.

Tremont-Lukats 2006 (score = 8.5)	Lidocaine	RCT	Supported by grant M01 RR03186 from the General Clinical Research Centers Program of the National Center for Research Resources, National Institutes of Health. No mention of COI.	N = 31 with peripheral neuropathic pain for at least 1 year, most (71.9%) with CRPS	Mean age is 39.8 years. 9 males, 22 females.	Six-hour infusion of 3 doses (1mg/kg, n = 7;, 3mg/kg, n = 9; 5mg/kg, n = 8) of lidocaine vs. placebo (n = 7). Follow-up at 0, 1, 2, 3, 4, 5, 6 8, and 10 hours.	Every 4 hours to a total of 10 hours.	At 4 hours, lidocaine 5mg/kg/hour favored over placebo and lasted to end of follow-ups. At 6 hours (end of infusion) proportion of responders was 28.6% receiving placebo, 14.3% 1mg/kg/hour, 22.2% lidocaine at 3mg/kg/hour, 50% 5mg/kg/hour.	"[O]ngoing neuropathic pain measured by PID and PID % was relieved during 6 hours of lidocaine infusion at 5 mg/kg/h, and relief continued for the additional 4 hours of observation. The lower infusion rates of lidocaine did not differ from placebo."	Short-term trial. Small sample size, each group <10; 10 hours duration. Insufficient follow-up to determine efficacy.
Kvarnström 2003 (score = 8.0)	Lidocaine	RCT	Supported by grants from the Swedish Medical Research Council grant no. 9077 (TG) and from Astra Zeneca R&D, So¨derta¨lje, Sweden. No mention of COI.	N = 12 with peripheral neuropathic pain of traumatic origin for at least 1 year	Mean age is 47 years. 3 males, 9 females.	Ketamine 0.4mg/kg vs. lidocaine 2.5mg/kg vs. saline each sessions separated by 1 week. All received each treatment. Follow-ups at 0, 15, 45, 60, 120, 150 minutes for each treatment.	Follow up at 1 week.	Difference in VAS reduction significant between ketamine and placebo (p = 0.009), not between lidocaine and placebo (p = 0.299) or ketamine and lidocaine (p = 0.076).	"Our conclusions from this study could be summarized in four points. 1. Seven out of 12 patients given ketamine and 4 out of 12 patients given lidocaine responded to treatment (according to our criterion of 50% reduction in pain) during and soon after infusion. This indicates the potential usefulness of these classes of drugs in the treatment of neuropathic pain. 2. Assessment of baseline data of somatosensory functions could not be used to identify responders to treatment to either drug. Neither did ketamine nor lidocaine give any specific	Small sample size. Short-term experiment with insufficient follow-up (2.5 hours) to determine efficacy.

									effects on sensory variables. 3. The high frequency of side-effects limits the clinical usefulness of ketamine and lidocaine. Further development of similar drugs is needed. 4. Ketamine and lidocaine seem to have a limited suitability as diagnostic tools for neuropathic pain as both their sensitivity and specificity for this objective are low."	
Kvarnström 2004 (score = 8.0)	Lidocaine	Crossover Trial	No mention of sponsorship or COI.	N = 10 with chronic pain after spinal cord injury, average 9 years duration	Mean age is 45 years. 9 males, 1 female.	Ketamine 0.4mg/kg vs. lidocaine 2.5mg/kg vs. saline placebo, each test sessions separated by 4 days. All received all treatments. Follow-up at 0, 15, 45, 60, 120, 150 minutes for each treatment.	Follow up at 4 hours.	VAS-reduction favored ketamine group over placebo group (p= 0.01). A significant difference in number of responders found in ketamine group over placebo group (p = 0.025).	"The present study provides evidence that the NMDA-antagonist ketamine yields substantial pain relief to patients with neuropathic pain below the level of SCI. The registered side-effects limit the clinical usefulness of the treatment. However, the high ratio of pain relief in this usually 'refractory' pain state raises interest in the development of NMDA-antagonists with a wider therapeautic ratio. Lidocaine, in the dose given in this study, did not give significant pain relief to this category of patients."	Small sample size. Short-term experiment with insufficient follow-up (2.5 hours) to determine efficacy for treatment
Galer 1996 (score = 7.5)	Lidocaine	RCT/Cross over Trial	Sponsored by NIH Pain Research Training Grant NS 07265. No mention of COI.	N = 9 with neuropathic pain (majority had diabetic neuropathy	Mean age is 51 years. 4 males, 5 females.	All received 2mg/kg and 5mg/kg intravenous lidocaine infusion (IVL) over 45	Follow up at 1 week.	Both treatments showed an improvement, but no differences between groups. Followed up with 4-	"[T]here was evidence of a dose-response relationship with IVL; pain relief was significantly greater with the higher lidocaine dose, although both doses	No placebo arm. Small sample size. Insufficient data to recommend

						minutes. Treatments at least 1 week apart. Study lasted 4 weeks.		week titrating trial of mexiletine beginning at 150mg BID for 1 week, 150mg QID for 1 week, 300mg TID for 1 week, then 300mg QID for last week. Mean mexiletine dose tolerate 878mg. Two reported no relief and did not tolerate maximum doses. Two reported "severe anxiety" at 450mg/day and not able to be titrated further. Pain relief with mexiletine predicted from pain relief with lidocaine infusion. Increasing pain prevented tapering of mexiletine among 4 patients at termination of study.	reduced pain VAS by a similar amount. The IVL response also correlated with response to subsequent administration of oral mexiletine. No association was found between reduction in allodynia and report of pain relief. With oral mexiletine, high doses or blood levels were not associated with greater degrees of pain relief."	either IVL or subsequent mexiletine.
Kastrup 1987 (score = 5.5)	Lidocaine	RCT	No mention of sponsorship. Jens Kastrup received a research fellowship from the University of Copenhagen. Palle Petersen received a research fellowship from	N = 15 with diabetic neuropathy	Mean age is 47 years. 9 males, 6 females.	5mg/kg body weight intravenous infusion of lidocaine vs. 1ml/kg body weight isotonic sodium chloride over 30-minute durations. All randomly received both treatments in	Follow up at 21 days.	Using FIS a beneficial effect seen at 1, 8, 15 days after lidocaine infusion ($p < 0.05$, $p < 0.02$, and $p < 0.10$). At 3 days more patients had reduction pain score greater than 15mm	"Intravenous infusion of lidocaine had a beneficial effect on the symptoms, but not on the signs of chronic painful diabetic neuropathy."	All DM neuropathy. Small sample size. Short-term follow-up (21 days). Insufficient follow-up for treatment recommendation.

			the Danish Heart Foundation.			5 week intervals. Follow-up 1, 8, 15, 22, 29, 35 days.		on VAS than placebo (p<0.05)		
Kastrup 1986 (score = 5.0)	Lidocaine	Crossover Trial	No mention of sponsorship. Jens Kastrup received a research fellowship from the University of Compenhagen.	N = 15 with painful diabetic neuropathy for 6 months to 20 years	Mean age is 47 years. 9 males, 6 females.	With an interval of 5 weeks, patients received both intravenous infusion of 5mg/kg body weight lidocaine and1ml/kg body weight isotone sodium chloride. Follow-ups before, day after, and once weekly for 5 weeks.	Follow up once weekly for 5 weeks.	Lidocaine relieved symptoms more effectively than placebo at Day 1 (p <0.05) and Day 8 (p <0.02) after infusion; 11 patients in lidocaine group showed reduced pain compared to 4 in placebo group, p <0.05.	"[I]ntravenous lidocaine infusion significantly relieved symptoms in 11 of 15 patients with long term, painful diabetic neuropathy. An improvement in metabolic regulation cannot explain the findings. Lidocaine might relieve symptoms, as in cardiac arrhythmias, by disconnecting abnormal nervous impulse circuits."	Report quite brief, precluding robust analysis of data and results. Some details sparse. No intermediate-to long-term follow-up.

Monoclonal Antibody Injection

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Bramson, 2015 A (score=8.0)	Monoclonal Antibody Injection	RCT	Sponsored by Pfizer Inc. CB, WC, DK, MTB, CRW, and KMV are employees of Pfizer Inc. and hold stock or stock options. DNH received compensation for consultation related to aspects of design of the diabetic peripheral	N = 73 patients with DPN.	Mean age of Treatment group: 61.6, Control group: 59.6. Sex(M:F) 47:26	Treatment (N=38) and control group (N=35) received sub-cutaneous tanezumab 20 mg or placebo, respectively, on Day 1 and Week 8.	Week 8 and 16	Mean differences in average DPN pain score favored the treatment group at week 4 and week 8 vs. the control group (p=0.009). Significantly more patients in the treatment group had greater than or equal to 30%, 50%, and 70% reductions in average DPN pain	"Tanezumab provided effective pain reduction in DPN. No new safety concerns were observed despite preexisting neuropathy."	Data suggest the highest dose of tanezumab provided effective pain reduction.

			neuropathy study. PJD receives an honorarium for being an Associate Editor of Diabetes. The authors had complete access to all of the data obtained in the study and had final responsibility for the decision to submit the article for publication.					scores at Week 8 (p<0.042)		
Makharita, 2015 (score=7.5)	Monoclonal Antibody Injection	RCT	No mention of COI or sponsorship.	N= 138 patients with acute thoracic herpetic eruption.	Mean age: 56.4 years; 65 males, 73 females	Patients received a paravertebral block using 10 ml saline (placebo group) (n=68) Vs. 25 mg bupivacaine, plus 8 mg dexamethasone in total volume of 10 mL (active group) (n=70) All patients received	At baseline, 3, 4, 12, 24 weeks	Significantly shorter duration of pain and herpetic eruption was noticed in the active group vs. placebo group (P = 0.013 and < 0.001, respectively). Active group showed significantly lower VAS at the third week. Significantly lower doses of pregabalin and acetaminophen were consumed in the active group. Incidence of PHN was comparable in both groups after 3 months (P = 0.094). A significantly lower	"Early single paravertebral blockade in the course of acute thoracic HZ seems to be a safe and effective adjuvant treatment modality."	Data suggest efficacy from single paravertebral injection evidenced by shorter duration of pain, fewer herpetic eruptions, lower VAS scores at 3 weeks and reduced consumption of pregabalin and acetaminophen.

						pregabalin 150 mg twice daily.		incidence of PHN was noted in active treatment group at 6 months (P = 0.048).		
Wang, 2014 (score=5.5)	Monoclonal Antibody Injection	RCT	Sponsored by Janssen Research & Development, LLC. Coi, one or more of the authors have received or will receive benefits for personal or professional use.	N=77 patients with peripheral neuropathic pain	Mean age: 58.7±9.48 years; 43 males, 34 females	Fulranumab 1 (n=16): received 1 mg dose subcutaneously into thigh or abdomen every 4 weeks vs Fulranumab 3 (n=14): received 3 mg dose subcutaneously into thigh or abdomen every 4 weeks vs Fulranumab 10 (n=23): received 10 mg dose subcutaneously into thigh or abdomen every 4 weeks vs Placebo (n=24):	12 weeks	At follow-up reduction of average pain intensity was LS=-1.2 (95% CI -2.44 to -0.06, p=0.04) for Fulranumab 10 compared to placebo. Mean reduction of average daily pain showed positive dose-response relationship (p=0.014, 1-sided).	"Despite early study termination, fulranumab treatment resulted in dose-dependent efficacy and was generally well tolerated."	Clinical study hold, data suggest some efficacy compared to placebo.
Van Wijck, 2006 (score=4.5)	Epidural Steroids	RCT	Sponsored by a grant from the Netherlands Organisation for Scientific Research (NOW number 945-02-009). No COI.	N=598 patients with acute herpes zoster	Mean age: 66 years; 234 males, 364 females	Epidural group (n=301): received standard therapy with one additional epidural injection of 80 mg methylprednisolone acetate and	1, 3, 6 months	After 1 month of treatment, 137 patients in epidural group reported pain and 164 patients in standard group reported pain (p=0.02). After 3 months of treatment epidural group had 58	"We conclude that one epidural injection of methylprednisolone and bupivacaine, applied in the acute phase of herpes zoster, has a modest effect in reducing zoster-	Standard care bias, data suggest only a modest effect from a single epidural injection of methylprednisolone plus bupivacaine vs standard care.

						10 mg bupivacaine vs Standard Group (n=297): received oral antivirals and analgesics		patients with reported pain and standard group with 63 patients (p=0.47). After 6 months, epidural group reported pain by 39 patients and standard group reported 44 patients (p=0.43).	associated pain for 1 month."	
Ji, 2009 (score=4.5)	Injection Therapy	RCT	Supported by grants from the National Natural Science Foundation of China (30870828 to YL; 30725039 to LX). No mention of COI.	N = 132 patients with acute herpes zoster.	Mean age of paravertebral group: 66, standard group: 68. Sex (M:F) 58:74	Standard group (N = 68) received 800 mg acyclovir, 5x per day for 7 days. Paravertebral group (N = 64) received paravertebral injections of 10 mL 0.25% bupivacaine and 40 mg methylprednisolone acetate every 48 hours for a week in addition to the same treatment as the standard group.	1, 3, 6, and 12 months	At 1 month follow-up 13% of paravertebral group patients reported pain compared to 43% of patients from the standard group. (p<0.001) Both groups experienced a non-significant increase in QOL.	"Repetitive paravertebral anesthetic block in combination with steroids plus standard treatment with acyclovir and analgesics significantly reduced the incidence of PHN than the standard treatment alone."	Standard care bias, data suggest incidence of PHN lower in injection group and zoster associated pain at 1 month was 13% vs 45% in standard care group.
Xu, 2013 (score=4.0)	Methylcobalamin Injection	RCT	No mention of sponsorship. No COI.	N = 80 patients with herpetic itching	Mean age: B_1 Group 60.5, B_{12} Group 62.7,	All groups: (N=20) injections received 1x per day, 6 days per	Day 7, 14, and 28	Thiamine yielded a significant itch relief, cobalamin yielded a significant pain relief, and their combination	"In conclusion, suggested that local thiamine injection had a significant antipruritic effect	Data suggest injections of methycobalamin was superior to other 2

					LD Group 61.8, COB Group 59.1 Sex(M:F) 38:42	week, for 4 weeks. B_1 Group received thiamine 100 mg local injections. B_{12} Group received methylcobalamin (cobalamin analog, 1000 ug in 2 mL ampoules) LD Group received 1.0% lidocaine (30 mg/3.0 mL COB Group received a combination of thiamine (100mg) and methylcobalamin (1000 mg).		significantly relieved both pain and itch; which all continued till the endpoint (all p<0.001). The activities of daily living and quality of life data at the endpoint were consistent with a significant benefit in the thiamine (p<0.05), cobalamin, and combination groups (both p<0.001).	on HI, local cobalamin injection had a significant analgesic effect, and combination of these 2 drugs had the dual effect, but no obvious synergies were observed. Local injection of combination of thiamine and cobalamin was observed as a critical intervention to relieve zoster-related itch and pain."	groups for pain relief.

Nerve Blocks

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Eker, 2012 (score=4.5)	Methylprednisolone	RCT	Sponsored by Baskent University and no COI.	N=88 patients with neuropathic pain.	Mean age: 54.8 years; 56 males, 32 females	Methylprednisolone group (n=44): received 80 mg depo-methylpredisolone plus 0.5% lidocaine in total of 10-20 mL solution vs Control group (n=44): received 0.5% lidocaine	3 months	NRS scores posttreatment were better for methylprednisolone group compared to control (p<0.0001). LANSS	"Our results suggest that peripheral nerve block with 80 mg depo-methylprednisolone plus 0.5% lidocaine provides effective management in the treatment of neuropathic pain due to peripheral nerve damage."	Sparse methods, data suggest at 3 months, pain socres were best in the combination treatment group.

Vitamin B12 & B1

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Xu, 2014 (score=5.5)	Vitamin B12 & B1	RCT	No mention of Sponsorship. No COI.	N = 80 patients with herpetic itching.	Mean age: 61; 41 males, 39 females.	B_1 Received thiamine, 100 mg n 1 mL ampoules. (n = 20) vs B_{12} Methylcobalamin, cobalamin analog 1000 micrograms in 2 mL ampoules. (N = 20) vs lidocaine. 1.0% lidocaine 30 mg/3.0mL (N = 20) vs B_1 + B_{12}, Combined thiamine and	28 days	B_1 vs B_{12} vs LD vs COB: < 30 % itch reduction 4 vs 18 vs 20 vs 2 ≥ 30 % itch reduction; 14 vs 2 vs 0 vs 12 ≥ 50 % itch reduction; 2 vs 0 vs 0 vs 8. Time effect on	"The study results suggested that the local cobalamin injection in the B12 group could significantly relieve the pain with HI."	Data suggest COB efficacy was not greater than the sum of either part (B1 +B12).

						methylcobalamin. (N = 20)		itching (p < 0.001) < 30 % pain reduction; 15 vs 2 vs 17 vs 1 ≥ 30 % pain reduction 5 vs 10 vs 3 vs 6 ≥ 50 % pain reduction 0 vs 8 vs 0 vs 13. Time effect on pain intensity (p < 0.001)		

VZV Injection

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Oxman 2005 (7.0)	VZV Injection	RCT	No mention of sponsorship or COI.	N=38,546 with a history of varicella or lived in US for 30+ years.	Mean Age: >60 years; not specified.	VZV vaccine – vaccine compromised of 24,600 plaque-forming units per dose. Vs. Placebo – placebo compromised of virus stablizers.	From 31 months to 65 months.	Zoster vaccine reduced the incidence of herpes zoster by 51% (p<0.001) and post-herpetic neuralgia by 66% (p<0.05).	"Thus the authors did not recommend the use of the current varicella vaccine to prevent the occurrence of herpes zoster and post-herpetic pain.	Data suggest VZV significantly reduced the incidence of HZ by 51% and reduced pain associated with PHN.

IV Infusions

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kanai 2010 (6.0)	IV Infusions	RCT	No mention of sponsorship or COI.	N = 24 patients with post-herpetic neuralgia.	Mean age: 73; 13 males, 11 females.	30 min rest in temperature control 20 degrees Celsius. Prostaglandi E1 (PGE) 60 micrograms in 100ml saline. Vs Placebo (PBO) 100 mL of saline. 7 day washout then crossover.	14 days.	PGE decreased VAS score ongoing pain 6.0 (m before treatment to 2.8 (P < 0.001) (PBO decreased the VAS score 5.5 to 5.0 (P < 0.001). Twelve of all 24 patients suffered from tactile allodynia. VAS was reduced by PGE therapy (P < 0.01) and PBO (P = 0.05). The effect of PGE treatment persisted for a median of 8 hours (range, 1–48 hours). PBO disappeared completely within 3 hours.	"Intravenous infusion of PGE produces analgesia associated with elevation of skin temperature in patients with PHN."	Crossover study. Data suggest IV PGE produced increased skin temperature and a reduction in pain intensity.
McCleane 1999 (5.5)	IV Infusions	RCT	No mention of sponsorship or COI.	N=20 patients with neuropathic pain.	Mean age: 40 years; 9 males, 11 females.	Group A (n=) - received 1000 mL placebo/saline infusion, followed 1 week later by an infusion of 15 mg/kg phenytoin (Parke	Daily for 1 week.	Pain scores after 2-Hr phenytoin infusion for shooting pain for +1 day – 2.69, p<0.05; +2 day – 3.37, p<0.05; + 4 days –	"This study indicates that phenytoin has a predominant effect on burning pain, shooting pain, numbness,	Data suggests IV phenytoin has analgesic properties for relief of neuropathic pain.

						Davis) in 1000 mL 0.9% saline under the same conditions. Vs. Group B (n=) - received the phenytoin infusion in week 1 and the placebo/saline infusion in week 2.		3.75, p<0.05. For sensitivity pain were +1 day – 3.87, p<0.05; +2 days – 4.27, p<0.05. For overall pain at +1-day score is 3.28, p<0.05.	sensitivity, and overall pain with no appreciable effect on paresthesia."	
Layman 1986 (5.0)	IV Infusions	RCT	No sponsorship. No mention of COI.	N=20 patients with post-herpetic neuralgia.	Mean age: 70 years; 6 males, 14 females.	Vincristine group (n=10) – 0.01% solution (2 mg in 20 ml) in 0.9% saline and 5% dimethyl sulphoxide administered to patients 3 times weekly for 4 weeks. Vs. Control group (n=10) – sterile 0.9% sodium chloride administered to patients 3 times weekly for 4 weeks.	6 weeks.	Post-treatment VAS scores for the vincristine group showed improvement in 8/10 participants. The mean score was 59%, an improvement from baseline score, p=0.05. At follow up, 7/10 in vincristine group improved on VAS score, mean of 27%, p=0.05. No patients in control group depicted improvement.	"'The work of Csillik and Fitzgerald has opened up a wider perspective in the role of axon transport in the aetiology and treatment of chronic pain. but the results of this present trial do not confirm the value of vincristine iontophoresis in the treatment of post-herpetic neuralgia of over 6 months duration."	Data suggest lack of efficacy.
Hong 2015	IV Infusions	RCT	No sponsorship or COI.	N=60 patients with painful diabetic	Mean age: 63.6 years; 28 males, 32 females.	Group A (n=20) – participants given a low dose of lipo-PGE1 following	3 weeks.	Group C's post-treatment VAS score is 4.14, compared with pre-	"High-dose lipo-PGE1 has better efficacy than low-dose lipo-PGE1 or	Data suggests best treatment response in higher dosage

(4.0)				peripheral neuropathy.		intravenous bolus injection of mecobalamin (MeCbl, 0.5 mg once daily (QD)) Vs. Group B (n=20) – participants given a high dose of lipo-PGE1 following intravenous bolus injection of mecobalamin (MeCbl, 0.5 mg once daily (QD)) Vs. Group C (n=20) – participants received MeCbl alone.		treatment data, P<0.05. Group A's post treatment VAS score is 3.28, p<0.05, compared with pre-treatment data and compared with control group. Group B's post treatment VAS score is 2.48, p<0.05, compared with pre-treatment data, control group, and treatment A. The total response rate (%) for the Group C, Group A, and Group B is 55%, 80%, and 90%, respectively.	MeCbl alone in the treatment of painful DPN."	lipo-PGE1 group although all 3 groups had varying levels of positive response.

AMPA Receptor Antagonist NS-1209

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Cousins 2013 (6.0)	AMPA Receptor Antagonist NS-1209	RCT	Sponsored by KAI Pharmaceuticals, Inc., manufacturers of KAI-1678. Dr. Pickthorn,	N = 23 patients with Postherpetic Neuralgia.	Mean age: 69.9 years; 17 males, 6 females.	KAI-1678 (n=21) – patients received a 25 mg total dose of KAI-1678. Vs.	Baseline and 6 hours.	The change in mean pain intensity from baseline to end of infusion in KAI-1678 is -1.0, in Lidocaine is -2.0, in Placebo is -1.1. The treatment comparison, lease squares mean	"We conclude that KAI-1678 is not efficacious as an acute analgesic for chronic neuropathic pain because of PHN. However, for the first time, the	Crossover design. Data suggest lack of efficacy of KAI-1678 for pain reduction. Lidocaine group had significant pain reduction

			Dr. Huang, and Dr. Bell are employees and stockholders of KAI Pharmaceuticals, Inc. Dr. Cousins has received consulting fees from KAI Pharmaceuticals, Inc.			Lidocaine (n=22) – patients received a 700 mg total dose of lidocaine. Vs. Placebo (n=22) – patients received a dose of 0.9% saline. Treatments were infused at rate of 2 mL/hour for the first hour and 1 mL/hour for the subsequent 5 hours.		difference in KAI-1678 vs Placebo is -0.21 (two-sided 90% CI -0.88 to 0.45) and in Lidocaine vs Placebo is -0.85 (two-sided 90% CI -1.5 to -0.2).	results demonstrate that subcutaneous infusions of lidocaine are effective in treating neuropathic pain. The results of lidocaine treatment also indicate that the crossover study design was adequate to detect a clinically meaningful response in this analgesia study."	at end of infusions.
Windebank 2004 (6.0)	AMPA Receptor Antagonist NS-1209	RCT	No mention of sponsorship or COI.	N=40 patients with distal neuropathic pain.	Mean age: 60.25 years;	Recombinant human IGF-I (n=20) – patients received 0.05 mg/kg twice daily by subcutaneous injection for 6 months. Vs. Placebo (n=20) – patients received by	No follow up.	The pain scores for IGF-I and Placebo were mean: 15 and 19; Median change: -0.285 and -0.35; mean change: -.0217 and 0.379; standard deviation: 1.856 and 2.637; range: -2.6-3.3 and -2.8-6.2, p=0.42, respectively.	"In conclusion, IGF-I was well tolerated but was not effective for treating idiopathic, painful neuropathy. The findings in this trial re-emphasize the power of the placebo effect. The results of controlled trials should be the only ones given weight	Data suggest lack of efficacy.

						subcutaneous injection for 6 months.			when assessing evidence supporting therapeutic agents for pain."	
Gormsen 2009 (5.5)	AMPA Receptor Antagonist NS-1209	RCT	Sponsorship by Neurosearch A/S, Ballerup, Denmark, that also provided NS1209. No mention of COI.	N=15 patients with chronic neuropathic pain.	Mean age: 54 years; 11 males, 4 females.	NS1209 (n=13) – patient received 322 mL NS1209 over 60 s followed by an infusion of 77 mL/h (77 mg NS1209) over 4 h + 100 mL saline infused during the last 30 min of the 4 h infusion. Vs. Lidocaine (n=15) – patients received 322 mL saline with B combine + 100 mL lidocaine (5 mg/kg lidocaine) during the last 30 min of the 4 h infusion. Vs. Placebo (n=13) – patient received 322 mL saline with B combine + 100 mL saline	No follow up.	NS1209 (-4.59, *P*<0.026) and lidocaine (-7.60, *P*<0.046) were significantly better than placebo in alleviating brush-evoked mechanical allodynia. NS1209 (-11.91, *P*<0.0486) and lidocaine (-11.00, *P* <0.0397) significantly reduced cold allodynia on the VAS. NS1209 did not differ from lidocaine in relieving neither brush-evoked allodynia (3.02, *P* <0.3716) nor cold allodynia (-0.91, *P* <0.8480).	"These findings are consistent with those reported for NS1209 in other models of pain and suggest that there is a role for AMPA receptor involvement in neuropathic pain in humans. Furthermore, NS1209 was safe and well tolerated at the given doses with a safety profile similar to placebo."	Cross over study. Small sample. Data suggests NS 1209 and lidocaine trended o be better than placebo.

						infused during the last 30 min of the 4 h infusion.				
Yousef 2013 (5.0)	AMPA Receptor Antagonist NS-1209	RCT	No sponsorship or COI.	N=80 patients suffering from chronic low back pain with a neuropathic component.	Mean age: 56.45 years; 53 males, 27 females.	Control (n=40) – Patients received placebo drugs administered using same dosing schedule as magnesium group. Vs. Magnesium (n=40) – Patients received an infusion of magnesium sulphate 1 g in 250 ml saline 0.9% for every 4 hours every day for 2 weeks. Then patients received oral magnesium therapy twice daily for 4 weeks.	3 and 6 months.	Numeric rating scale score for control and magnesium groups pretreatment were 7.4 and 7.5, p=0.06 between groups, respectively. At 2 weeks: 3.6 (p=0.036) and 3.4 (p=0.022), p=0.28 between groups, respectively. At 6 weeks: 6.6 (p=0.26) and 3.9 (p=0.029), p=0.003 between groups, respectively. At 3 months: 6.8 (p=0.51) and 4.4 (p=0.016), p=0.045 between groups, respectively. At 6 months: 7.2 (p=0.25) and 4.7 (0.034), p=0.027 between group, respectively.	"We believe that the use of magnesium presents a viable treatment option for patients with refractory chronic back pain who have failed to respond to conventional treatment."	Data suggests 2 weeks of IV magnesium followed by 2 weeks of oral magnesium can reduce pain and increase mobility.
Brill 2002 (5.0)	AMPA Receptor Antagonist NS-1209	RCT	No mention of sponsorship or COI.	N= 7 patients with postherpetic neuralgia.	Mean age: 70.3 years; 2 males, 5 females.	Magnesium (n=7) – patients received an IV infusion of magnesium sulphate 30 mg	Baseline, 10, 20, and 30 minutes.	Pain scores for the difference between magnesium and placebo at 10 minutes is 1.9 (p=0.063, 0-5 95%	"The present study supports the concept that the N-methyl-D-aspartate receptor is involved in the	Crossover study. Data suggest pain score were lower for magnesium groups but not

						kg^{-1} over a 30-minute period. Vs. Placebo (n=7) – patients received and IV infusion of 0.9%saline 100 ml over a 30-minute period. One-week washout period between both treatments.		CI), at 20 minutes is 2.4 (p=0.017, 1-5 95% CI), at 30 minutes is 3.1 (p=0.017, 1-7 95% CI).	control of postherpetic neuralgia"	after 10 minutes.

Systemic Adenosine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Sjölund, 2001 (score=5.0)	IV therapy	RCT	Sponsored by grants from the Swedish Medical Research Council (project no. 7485 to A.S. and 9077 to T.G.) and Karolinska Institutet. No mention of COI.	N=26 patients suffering with peripheral neuropathic pain	Mean age: 45.7 years; 5 males, 21 females	All patients received both treatments. Adenosine group: received 50 µg/kg/min for 60 min vs Placebo group: received isotonic mannitol for 60 min	Post treatment approximately 2 weeks	Spontaneous pain was reduced by adenosine group (p=.006) compared to placebo (p=.102). TPT in allodynic area increased for placebo group by 15% compared to adenosine group by 71% (p=0.045; p=0.0005, respectively).	"(t)his multi-centre, double-blind, placebo-controlled study demonstrates that systemic ADO treatment significantly reduces the area of dynamic tactile allodynia associated with peripheral neuropathic pain in	Crossover trial, data suggest tactile allodynia decreased in adenosine groups, but neither group improved tactile or spontaneous pain scores.

									parallel with subjective improvement of the clinical pain out-lasting the infusion."	

IV Lidocaine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Tremont-Lukats, 2006 (score=8.5)	IV Therapy	RCT	Sponsored by grant M01 RR03186 from the General Clinical Research Centers Program of the National Center for Research Resources, National Institutes of Health. No mention of COI.	N = 32 with peripheral neuropathic pain for at least 1 year, most (71.9%) with CRPS	Mean age: 39 years; 9 males, 22 females	Six-hour infusion of 3 doses (1mg/kg, n = 7;, 3mg/kg, n = 9; 5mg/kg, n = 8) of lidocaine vs. placebo (n = 7). Follow-up at 0, 1, 2, 3, 4, 5, 6 8, and 10 hours.	10 hours	At 4 hours, lidocaine 5mg/kg/hour favored over placebo and lasted to end of follow-ups. At 6 hours (end of infusion) proportion of responders was 28.6% receiving placebo, 14.3% 1mg/kg/hour, 22.2% lidocaine at 3mg/kg/hour, 50% 5mg/kg/hour.	"[O]ngoing neuropathic pain measured by PID and PID % was relieved during 6 hours of lidocaine infusion at 5 mg/kg/h, and relief continued for the additional 4 hours of observation. The lower infusion rates of lidocaine did not differ from placebo."	Data suggest PID % was significant in lidocaine group. Data suggest lidocaine was not superior to placebo at lower doses.
Attal, 2004 (score=5.0)	IV Lidocaine	RCT	Sponsored by l'Institut UPSA de la Douleur. No mention of COI.	N=22 patients in pain due to peripheral nerve injury	Mean age: 50.9±16.7 years; 14 males, 8 females	Lidocaine group: received 5mg/kg IV for 30 minutes vs Placebo group: received saline (0.9% NaCl) same volume for 30 minutes. All patients received	12 months	Mean intensity of pain for lidocaine group changed from pre-injection of 54±15.5 to 19±22 60 minutes post-injection compared to placebo from 54±15.4 to 38±22.Lidocaine group showed ≥50%	"These data indicate modality-specific antihyperalgesic effects of IV lidocaine in patients with peripheral nerve injury. Patients with mechanical allodynia may be	Crossover study, data suggest drug responses are dependent upon group of PN symptoms.

						mexiletine on an open basis titrated from 400-1000 mg per day following randomization.		improved pain intensity in 5 patients for up to 7 days compared to placebo with 0 patients. Sixteen patients showed decreased mechanical pain thresholds to von Frey hairs on painful side (p=.01).	good candidates for treatment with local anesthetic-like drugs and possibly with other sodium-channel blockers."	

IVIG & IV-VZV-IG

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hügler, 2002 (score=7.0)	IV-VZV-IG	RCT	No mention of sponsorship or COI.	N=20 patients with post herpetic neuralgia.	Mean age: 69.6 years; 18 males, 22 females.	VZV-IG (n=20) – patients received single intravenous infusion of VZV-IG in a dose of 2 mL/kg body weight. Vs. Control (n-20) – patients received a single intravenous infusion of human albumin 5% in a dose of 2 mL/kg per body weight.	42 days.	The Mean VAS score and 95% Coincidence Interval in the VZV-IG group at day 0 and day 42 were 45.00 (33.17; 56.82) and 13.28 (4.35; 22.20), respectively. In the control group the scores at day 0 and day 42 were 58.70 (41.99; 75.40) and 28.37 (16.38; 40.35), respectively.	"The results can be summed up by saying that VZV-IG not only reduces the incidence of PHN, but also that in certain respects the patients' assessments of their pain experience were different."	Long term data is needed to support short term outcomes but VZV-IG "appears" to decrease the incidence of PHN.

Jann, 2012 (score=5.0)	IV Therapy	RCT	No mention of COI. Sponsored by Grifols.	N=20 patients with painful neuropathy	Mean age: 66.5±7.5 years; 13 males, 6 females	IVIG therapy (n=10): receive adjuvant intravenous immunoglobulin (2 g/kg) in addition to regular therapy. vs Conventional Therapy (n=10): received anticonvulsants (4 took pregabalin, 1 took gabapentin, 1 took oxcarbazepine,1 took combo of gapapentin and duloxetine	60 days	The conventional therapy group showed VAS (mm) scores of 85.0±11.5 and 88.0±13.2 for the IVIG group at baseline. At visit 2, 5 days, the scores for IVIG and CT group were 49.6±13.0 mm (p<0.01) and 78.5±8.5 mm, respectively. VAS scores for the IVIG group at visit 3 and 4 were 28.8±15.2 mm (p<0.01) and for CT group remained similar to visit 2.	"This unblended pilot study showed a beneficial effect of IVIG on neuropathic pain intensity and quality of life in patients resistant to conventional treatments."	Standard care bias, data suggest significant sustained improvement in IVIG group at 4 weeks post treatment.

IV Acyclovir

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Acosta, 2001 (score=4.5)	IV Acyclovir	RCT	Sponsored by grants P30-AI 27767-12 from the National Institutes of Allergy and Infectious Disease and MO1	N=10 patients with persistent postherpetic neuralgia	Mean age: 67.4±13.8 years; 5 males, 5 females	IV Acyclovir Group (n=6): vs Oral Acyclovir Group (n=7):	14 days	Only 1 patient had positive clinical outcome with a consistent decrease in pain. No clinical benefit of acyclovir was established for this small sample.	"Acyclovir does not appear to be useful for the treatment of established postherpetic neuralgia based on the findings from this small group of	Small sample, data suggest lack of efficacy.

			RR00400 from the National Institutes of Health Center Research Resources, by the Minnesota Medical Foundation, and by the International Center for Antiviral Research and Epidemiology. No mention of COI.						patients. One of the five patients who received both high-dose intravenous and oral acyclovir reported a clinical benefit, and this individual was the only one of 10 volunteers who reported a consisten improvement in severity of pain."	

Ketamine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kvarnström 2003 (score = 8.0)	Ketamine	RCT/Cross over	This work was supported by grants from the Swedish Medical Research Council grant no. 9077 (TG) and from Astra Zeneca R&D, Sodertalje, Sweden. No mention of COI.	N = 12 with neuropathic pain	Mean age is 47 years. 3 males, 9 females.	Ketamine 0.4mg/kg vs. lidocaine 2.5mg/kg vs. saline. Duration of follow-up 160 minutes.	Follow up of 1 week.	Post-op pain (n = 9), trauma operations (n = 2), and disc hernia (n = 1). Mean reductions in VAS scores: ketamine 55%, 34% lidocaine, 22% placebo. Fifty percent or greater response rates found for 58.3% ketamine vs. 33.3% lidocaine vs. 16.7% of placebo. Adverse effects (ketamine/lidocaine /placebo):	"Ketamine showed a significant analgesic effect. The clinical usefulness is, however, limited by disturbing side-effects."	Response rate too low to use tests for diagnostic purposes. Small sample size. Short term follow up of IV medication trial demonstrated no difference between placebo and lidocaine and rapid benefit with ketamine, but rapid return

								somnolence (100/75/33%), light-headedness (75/42/8%), out-of-body sensation (67/34/0%), nausea (33/25/8%), paraesthesia, (83/17/0%) and unpleasant experience (50/8/17%).		to baseline after administration. Results limited to a clinical study.
Kvarnström 2004 (score = 8.0)	Ketamine	RCT/Cross over Trial	No mention of sponsorship or COI.	N = 10 with chronic pain after spinal cord injury that averaged 9 years duration	Mean age is 45 years. 9 males, 1 female.	Ketamine 0.4mg/kg vs. lidocaine 2.5mg/kg vs. saline placebo.	4 day follow up for 3 sessions.	At least 50% reductions in VAS scores during infusions were found during 50% of ketamine, 10% of lidocaine and 0% of placebo infusions.	"Ketamine but not lidocaine showed a significant analgesic effect in patients with neuropathic pain after spinal cord injury. The pain relief was not associated with altered temperature thresholds or other changes of sensory function."	Short-term study of IV medication. Requires longer term follow-up to determine if significant efficacy. Very short experiment. Spinal cord injury patients.

Intrathecal/Epidural Drugs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Rijsdijk 2012 (Score = 6.0)	Intrathecal	RCT	No mention of Sponsorship or COI.	N = 10 with postherpetic neuralgia.	Mean age; 73.6 years; 4 males, 6 females.	MPA + lidocaine. 4 intrathecal injections with 60 mg MPA + 60 mg lidocaine.	1, 4, 8 weeks.	Treatment group at 8 weeks Global pain increase by 0.6 on VAS. Vas control vs	"Considering the absence of clinical benefits and the potential risks of the treatment,	Small sample data suggest each of clinical efficacy and is not recommended

						(N = 6) vs Lidocaine 60 mg Lidocaine alone. (N = 4)		treatment. Higher vas in treatment group (P = 0.002).	intrathecal administration of MPA is not recommended."	due to concerns over safely and treatment
Kikuchi 1999 (Score = 6.5)	Intrathecal & Epidural	RCT	Sponsorship by grants for scientific research from department of education. No mention of COI.	N = 25 patients with postherpetic neuralgia (PHN).	Mean age: 65 years; 11 males, 14 females.	All premedicated with 10 mg Diazepam orally and 75 mg roxatidine 2 hours before treatment. Intrathecal methylprednisolone acetate (MPA). 3 mL of 2% lidocaine containing 60 mg MPA into intrathercal space. 60 mg contained 43.5 mg polyethylene glycol, 0.3 mg myristyl-y-pi-colinium chloride. (N = 14) vs Epidural MPA. 5 mL of 2 % lidocaine containing 60 mg MPA. (N = 15)	24 weeks	Epidural vs Intrathecal at end for excellent global pain relief. 3 vs 12 ($p < 0.01$).	"Our results suggest the effectiveness of intrathecal as compared to epidural MPA for relieving the pain and allodynia associated with PHN. Also, our findings, together with the decrease in IL-8, may indicate that intrathecal MPA improves analgesia by decreasing an ongoing inflammatory reaction in the CSF."	Data suggest intrathecal MPA appears to be a better analgesic than epidural MPA in patients with retractable PHN.

Eisenach 2003 (score=4.0)	Intrathecal	RCT	Sponsorship by grants from National Institutes of Health. No mention of COI.	N = 7 patients with chronic neuropathic pain.	Mean age: 37 ± 6; 3 males, 4 females.	Intrathecal adenosine (2 mg diluted in preservative free saline) and intravenous saline (100 mg) vs. intrathecal saline and intravenous adenosine (2 mg). Intravenous injections were performed over 4 h by infusion pump. Intrathecal injection was performed at a mid- or low lumbar interspace using sterile technique and #27 Whitacre spinal needle.	24 hours	Intrathecal adenosine statistically significant reduced the area of allodynia to testing with a cotton wisp. Intrathecal adenosine also reduced elicited pain from von Frey filament probing (p=0.04, by one way ANOVA). No effects were seen for intravenous adenosine or for intrathecal adenosine with a two way ANOVA.	"[I]intrathecal, but not intravenous adenosine produced a modest reduction in some aspects of hypersensitivity, including pain from stimulation in the area of hyperalgesia and reduced area of allodynia in patients with neuropathic pain."	Double blind crossover study. Small sample. Data suggest intrathecal adenosine improves pain and reduces allodynia from NP pain but intravenous adenosine in the same does not.

Epidural Clonidine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Reuben 2004 (score = 7.5)	Clonidine	RCT	No mention of sponsorship or COI.	N = 84 with history of upper extremity CRPS	Mean age is 49.5 years. 17 males, 67 females.	Intravenous regional anesthesia with 0.5% lidocaine (IVRA-L) 1mL NS	16 months for IVRA-C and 19 month for IVRA-L.	Recurrence rate of CRPS significantly lower in patients receiving IVRA with lidocaine and	"Intraoperative IVRA with lidocaine and clonidine on patients with a history of CRPS can	No differentiation between CRPS I or II. No mention of co-

				undergoing surgery on affected extremity		added to IVRA solution (n = 42) vs. intravenous regional anesthesia with clonidine 1µg/kg (IVRA-C) (n = 42).		clonidine vs. IVRA lidocaine only, p <0.001.	significantly reduce the recurrence rate of this disease process."	interventions during follow-up period.
Rauck 1993 (score = 5.0)	Clonidine	Crossover Trial	Supported in part by a grant from Fujisawa Pharmaceutical. No mention of COI.	N = 26 with RSD	Mean age is 38 years.	Normal saline vs. 300µg clonidine vs. 700µg clonidine with follow-ups at 20, 40 60, 120, 180, 240 and 360 minutes after injection.	Followed up weekly for 43 days.	McGill scores decreased with placebo from 36.0 to 35.7; in 300µg from 38.0 to 29.9; and 700µg dose from 37.2 to 25.7.	"[E]xtensive analgesia may be obtained by epidural administration. Sedation and hypotension may limit bolus epidural clonidine administration for RSD. The role for chronic epidural infusion of clonidine has not been established."	Blinding not well described; no long-term results reported despite continued treatment offered. Longer term infection complication rate of 31.6% (1 case of meningitis) over 40 days treatment is concerning.

Epidural Methylprednisolone (PINE Study)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Van Wijck 2006 (score = 4.5)	Intrathecal & Epidural	RCT	No COI	598 patients with acute herpes zoster rash	All 50 years of age or older , mean age of 66. 61% females and 39% males.	A single epidural injection of 80 mg of methylprednisolone plus 10 mg bupivicaine compared to standard care of	1, 3 and 6 months	At one month, 48% of epidural reported pain compared to 58% in control group.	"One epidural injection of methylprednisolone and bupivicane applied in the acute phase of herpes zoster has a modest effect at reducibng zoster-associated	Standard care bias. Data suggest only a modest effect for reduction of zoster associated pain from a single epidural

						oral antivirals and analgesics.			pain for 1 month. However, because this treatment did not prevent long-term postherpetic neuralgia, we suggest that an epidural injection of corticosteroid and bupivicaine only be considered for patients with severe acute pain from herpes zoster who are not responding to standard analgesic therapy."	injection of methylprednisolone plus bupivicaine plus standard care for up to one month.

Intrathecal Methylprednisolone & Midazolam

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Dureja, 2010 (score=6.5)	Benzodiazepams Midazolam and Prednisolone	RCT	No COI or sponsorship.	N=150 patients with pain and allodynia	Mean age: 57.4 years; 79 males, 66 females	M-O (n=49): received methylprednisolone (60mg) suspended in 10 mL of normal saline in the epidural space and preservative free normal saline 2 mL in the intrathecal space vs M-1 (n=48): received normal saline 10 mL in the	12 weeks	Groups M-1 and M-2 patients reported better pain relief compared to M-O group. M-2 Group showed better scores of pain and allodynia compared with patients M-O and M-1.	"The combination of intrathecal midazolam with epidural methylprednisolone resulted in prolonged duration of analgesia in patients with post herpetic neuralgia of lumbosacral dermatomes due to the complementary anti nociceptive	Data suggest combining epidural methyl prednisolone with intrathecal midazolam prolonged the analgesic effect in post herpetic neuralgia and decreased other analgesic use.

						epidural space and midazolam 2 mL (1 mg/mL) in the intrathecal space vs M-2 (n=48): received methylprednisolone (60mg) suspended in 10 mL normal saline in the epidural space plus midazolam 2 mL (1mg/mL) in the intrathecal space			action of intrathecal midazolam with epidural methylprednisolone on spinal nerve roots."	

Motor Cortex Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Radic, 2015 (score=4.0)	Motor Cortex Stimulation	RCT	Julia Radic, Ian Beauprie, and Paula Chiasson do not have anything to disclose. Zelma Kiss has the following disclosures: AHFMR, Researcher, Salary grant; AIHS, Researcher, Salary grant. Robert	N= 12 subjects with three different neuropathic pain syndromes who had placement of MCS systems	Mean age: 36.58 years; 9 males, 3 females	Patients received Low ("sub therapeutic") Vs. High ("therapeutic") stimulation for 12 weeks, followed by a crossover to the other treatment	12 weeks	The trial was halted early due to lack of efficacy. One subject withdrew early due to protocol violation and five subjects withdrew early due to transient adverse events. Six subjects with upper extremity pain completed the study. There was no	"We failed to show that MCS is an effective treatment for refractory upper extremity neuropathic pain and suggest that previous studies may have been skewed by placebo effects, or ours by nocebo. We suggest that a healthy degree of	Crossover study. Small sample, high dropout rate. Data suggest lack of efficacy of MCS.

			Brownstone has the following disclosures: CIHR, Researcher, Research support; CFI, Researcher, Research support; CRC, Researcher, Research support; NSRIT, Researcher, Research support.			group for 12 weeks.		significant change in VAS with low or high stimulation and no significant improvement in any of the outcome measures from low to high stimulation. SF-36 role physical and mental health scores were worse with high compared to low stimulation (p=0.024, p=0.005).	skepticism is warranted when considering this invasive therapy for upper extremity pain syndromes."	

Spinal Cord Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
de Vos 2014 (score=4.0)	Spinal cord stimulation	RCT	Sponsored by St. Jude Medical. Author Meier received teaching fees from St. Jude Medical and is a paid consultant for Biolab Technology.	N = 60 with painful diabetic neuropathy	Mean age: 58 for SCS group, 61 for control; 38 males, 22 females.	Spinal cord stimulation (SCS) - one electrode lead (Octrode or S8 Lamitrode) implanted in epidural space and positioned where patient reported optimal overlap between paresthesia and painful area (n = 40) vs. control (n = 20)	1, 3 and 6 months	Mean pain visual analog scale score at baseline and at 6 month follow-up, respectfully: SCS - 73, 31 (p<0.001, significant treatment effect within group), Control 67, 67 (p<0.0001, significant treatment effect between groups)	"In patients with refractory painful diabetic neuropathy, spinal cord stimulation therapy significantly reduced pain and improved quality of life."	Standard care bias. No sham procedure group nor blinding which likely biased results. Six month trial.

Stellate Ganglion Block

Stellate Ganglion BlockAuthor Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Makharita 2012 (score=7.0)	Invasive Treatment	RCT	No sponsorship or COI.	N = 61 patients with acute facial herpes zoster (HZ).	Mean age: 59.6 ± 3.2 years; 27 males, 34 females.	Group 1 placebo group received 8mL saline (N = 30) vs Group 2 received 8mL total of 8mg of dexamethasone and 6mL of bupivacaine 0.125% (N = 31). Stellate ganglion block was received by syringe 2X per patient with 1 week in between. Patients also received 150mg of pregabalin 2X/day.	Follow-up at baseline, 1, 2, 3, 4, 5 weeks, and 2, 3, and 6 months.	Significant results were seen in group 2 for shorter duration of pain (P=0.035), and at 3 and 6 months there were significantly lower postherpetic neuralgia (PHN) incidences in group 2 (P=0.043, P=0.035 respectively). Patient satisfaction at month 3 and 6 was significantly higher in Group 2 (p=0.03, P=0.004 respectively). VAS scores were significantly lower for group 2 at weeks 1, 2, 3, 4 (all P<0.001), 6, and months 2, 3, and 6 (P=0.014, P=0.015, P=0.007, P=0.042 respectively). Group 2 also had significant less intake of analgesic consumption per week (P<0.001)	In conclusion, for acute HZ of the face, early stellate ganglion blockade, in combination with an antiviral agent, is a very effective treatment modality that dramatically decreases the intensity of acute pain and shortens its duration. We believe it has preventive effects on PHN via reversing or preventing profound sympathetic stimulation and vasoconstriction, hence restoring intraneural blood flow and preventing nerve ischemia and damage.	Data suggest early stellate ganglion block when combined with antiviral can decrease the intensity of acute pain and decrease duration and incidence of postherpetic neuralgia.

Surgical Decompression

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size/Population:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
van Maurik 2014 (score=4.5)	Surgical Decompression	RCT	Supported by a grant from NutsOhra, a foundation for financial support in health care research, based in Amsterdam, The Netherlands. No COI.	N = 38 patients with painful diabetic neuropathy.	Mean age is 62.7 years. 22 males, 16 females.	All participants underwent surgical decompression of lower extremity nerves. Randomization occurred in which leg would receive the procedure (n = 38).	12 month follow up.	There was a significant overall difference between intervention and control leg scores over the 12-month follow-up period (p=0.004). At 12 months the difference between the control and intervention group had increased 1.8 (p=0.002). 73.7 percent of patients improved in visual analogue scale score. Surgical skills did not seem to have any statistical significance.	"Decompression of the nerves of the lower extremity in patients with painful diabetic polyneuropathy significantly decreases pain symptoms."	No blinding which could potentially bias results. No sham surgery group.

Tumor Necrosis Factor-Alpha Blockers

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size/Population:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Korhonen 2005 (score = 8.0)	Tumor Necrosis Factor-Alpha Blockers	RCT	Supported by a grant from Centocor, Inc, Malvern, PA. Corporate/Industry	N = 40 with moderate or severe	Mean age is 40.7 years. 24	Infliximab 5mg/kg (n = 21) vs. placebo (n =	Follow up at 12 weeks.	"A significant reduction in leg pain was observed in both groups, with	"The results of this randomized trial do not support the use of infliximab	Follow-up report with 1-year observation data reported

			funds were received in support of this work. One or more of the author(s) has/have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this manuscript: e.g., honoraria, gifts, consultancies.	sciatic pain	males, 16 females.	19) for 12 weeks.		no significant difference between treatment regimens." No significant differences between groups.	for lumbar radicular pain in patients with disc herniation-induced sciatica."	that 67% of infliximab group pain free vs. 63% placebo.

Ziconotide

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size/Population:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Wallace, 2006 (score=6.5)	Ziconotide	RCT	Sponsored by Elan Pharmaceuticals, Inc. COI: M.M., D.M., and D.E. were employees of Elan Pharmaceuticals during the conduct of this trial.	N = 264 patients with severe chronic nonmalignant pain	Mean age: 52 years, 143 males, 112 females	Ziconotide (n=170) vs Placebo (n=87)	6 days	Ziconotide group showed a higher percent change in VASPI score compared to placebo ($p \leq 0.001$). VASPI score for ziconotide group improved by 31.2% (95% CI 24.6-37.9) compared to placebo of 6% (95% CI 0-11.9).	"Ziconotide provided significant analgesia in patients for whom conventional therapy failed. However, there was a considerable incidence of ziconotide-associated AEs due to the rapid titration and high doses administered."	Trial of 6 days. Data suggest intrathecal use may provide short-term relief where intrathecal opioids have failed.

Prognosis

The prognosis for neuropathic pain is largely determined by the cause and the ability to treat or remove the underlying cause, or causes if multiple. For occupational toxicological causes, the prognosis is generally for slow recovery if exposure ceases. This means that permanent workplace restrictions are usually employed. Similarly, for diabetic neuropathy, intensive management of glucose control generally stops progression and sometimes improve symptoms of neuropathy. For alcoholic neuropathy, abstinence often slowly reverses the disease. For autoimmune processes, progressive disease usually results, as these are usually untreatable unless related to a treatable rheumatological disorder.

For radicular spine conditions, see the respective spine guidelines.

Differential Diagnosis

The differential diagnosis of neuropathic pain is extensive. Below are the more common causes, rather than a complete list.

- Diabetic neuropathy
- Alcoholic neuropathy
- Autoimmune neuropathies
- Stroke pain
- Multiple sclerosis pain
- Amputation
- Peripheral nerve injury
- Radiculopathy
- Radiculitis
- Herpes zoster/Shingles
- HIV/AIDS
- Hypothyroidism
- Nutritional deficiencies
- Pernicious anemia
- Guillain-Barre Syndrome
- Intracranial aneurysm
- Bell's palsy
- CNS tumor
- Idiopathic

Complications / Comorbidities

- Diabetes mellitus
- Alcohol
- Autoimmune disorders
- Nutritional deficiencies
- Pernicious anemia
- Herpes zoster/shingles

Follow-up Care

It is **Recommended (I)** that patients with work-related neuropathic pain should have a follow-up visit every 1 to 2 weeks initially by a new health care provider or while still out of work. Appointments should generally be time-contingent, i.e., scheduled as opposed to obtained secondary to changes in pain complaint. The initial appointments should focus on identify remediable causes of neuropathic pain and exposure elimination, if a neurotoxin is identified.

Initial visits should include an ongoing focus on function, obtaining more information from the patient, confirming that the history information is consistent, observing for injury/illness behaviors, confirming the diagnosis, and assessing the need for psychological referral and evaluation. The educational process of informing the patient about functional status and the need to engage in a functional rehabilitation program focusing on restorative exercises should be reinforced. These restorative exercise program components should be labeled the cornerstone of the medical management plan for the patient's pain. Other means of managing pain, including pharmaceuticals should be addressed. Initial visits for chronic pain should also include information to avoid bed rest, excessive rest or appliances. The provider should take care to answer questions and make these sessions interactive so that the patient is fully involved in his or her recovery.

Subsequent follow-up is **Recommended (I)** to be less frequent, and tailored to the patient's needs. In cases where the patient is at work, fully functional and on minimal or steady-state maintenance NSAID medications, follow-up every 6 to 12 months is **Recommended (I)**. However, in the active rehabilitation phase for patients with neuropathic pain, follow-ups weekly for as much as 2 or 3 months is **Recommended (I)** to also be conducted if there is need for physical therapy and occupational therapy to sustain a team-oriented focus on restoration and achievement of functional goals.

Job Analysis

The primary purpose of job analyses for patients with neuropathic pain is to identify and catalog all chemicals used in the workplace. This usually begins with a patient history, then supervisor interview, and subsequently obtaining Safety Data Sheets. This is followed by a careful evaluation of whether there is a known neurotoxin. In cases where a neurotoxin is identified, complete removal from exposure is indicated.

For radicular pain, see Low Back Disorders and Cervical and Thoracic Spine Disorders Guidelines.

Chronic Pain Rehabilitation

Summary of Recommendations

The following summary table contains recommendations for rehabilitation from the Evidence-based Chronic Pain Panel. These recommendations are based on critically appraised higher quality research evidence or, when such evidence was unavailable or inconsistent, on expert consensus as required in ACOEM's Methodology. Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient – Recommended (Consensus-based), "I" Level
- Insufficient – No Recommendation (Consensus-based), "I" Level
- Insufficient – Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

Work Conditioning, Work Hardening, Early Intervention Programs and Back Schools for Chronic Pain	Recommended, Insufficient Evidence (I)Recommended, Insufficient Evidence (I)
Tertiary Pain Programs: Interdisciplinary Pain Rehabilitation Programs, Multidisciplinary Rehabilitation Programs, Chronic Pain Management Programs, and Functional Restoration Programs	Recommended, Evidence (C)Recommended, Evidence (C)
Participatory Ergonomics Programs for Patients with Chronic Pain	Recommended, Evidence (C)Recommended, Evidence (C)

Overview

There are numerous different types of rehabilitation programs. To help organize and present a hierarchical construct, rehabilitation is classified in this Guideline as primary, secondary, or tertiary.

Primary rehabilitation includes the most widely encountered therapy and consists of a relatively minimal quantity(ies) of medical care coupled with physical therapy, occupational therapy or healthcare provider directed exercises (i.e., a home exercise program). While there is much diversity, typical strategies commonly include teaching specific stretches, graded exercises, addressing fear avoidant beliefs ("kinesiophobia"), and advancing activity levels, generally in the acute to subacute phases, until recovery is complete. There are many quality trials evaluating these treatments and specific guidance for primary rehabilitation is included with each disorder (please see individual ACOEM Guidelines). Particularly when there are questions about the physical job demands and to quantify the gap(s) between the job demands and patient's capabilities, there should delineation of the required work tasks through conversations with the patient and employer.

Secondary rehabilitation usually occurs after either failure of primary rehabilitation and/or a determination that the healing course will not result in bridging a gap between current abilities and job physical demands. Secondary rehabilitation includes more advanced and contact time-intensive rehabilitative treatments and are most commonly termed Work Conditioning and Work Hardening. Back Schools are a specific program element in this category. Early Intervention programs are another type of secondary rehabilitation program that is sometimes used. Work Conditioning usually emphasizes exercises and includes tasks to simulate work activities. Work Hardening typically includes progressive exercise but adds some limited psychological counseling and education. There are quality trials of Back Schools, but there is little quality literature supporting Work Conditioning and Work Hardening programs. Guidance is included in this section.

Tertiary rehabilitation involves interdisciplinary rehabilitation. There are many different terms and emphases of tertiary rehabilitation programs; however, they can generally be classified into pain programs and functional restoration programs. These programs generally employ multiple disciplines using biopsychosocial approaches to address pain, function, work, and psychological distress. By contrast, acute injuries are treated with acute care paradigms of utilizing specific treatment(s) for cure of a discrete diagnosis. There are some quality trials of tertiary rehabilitation programs and guidance is included in this section.

Initiation of these programs may be considered in the subacute stage if disability is not adequately explained by physical findings and primary rehabilitation treatments have failed to significantly improve the functional status. Chronicity by itself is a major predictor of poor outcome.[88] The longer it takes to resolve the disability (delayed recovery), the higher the cost, the more likely patients are to never return to work, the greater the risk for costly medical care, and the greater the likelihood for costs to be shifted from the workers' compensation system to other payment systems (e.g., long-term disability, Social Security Disability Insurance). The increased costs of rehabilitation programs may be justified by cost benefit analysis of program outcomes. Consistent with the above, earlier intervention programs may be reasonable.

Functional restoration is both a type of interdisciplinary pain management and rehabilitation program, as well as a general approach to medical care. Fundamental elements of a functional restoration approach include assessment of the patient's dynamic physical and functional status including traditional tests for strength, sensation, and range of motion. Psychosocial strengths and stressors must also be assessed (including a history of childhood abuse, anger, fear of reinjury, and a history of substance misuse), and the patient's support system, evidence of mood disorders, assessment of education and skills, medication use, presence of litigation, and work incapacity analyzed. Following this evaluation, the emphasis is on expectation management, directed conditioning and exercise, CBT, functional goal setting and decrease in medication use. An ongoing assessment of patient participation and compliance (with documentation of complicating problems and progress toward specific goals, including reduction in disability and medical utilization) is needed.

In functional restoration, the treatment team functions more as educators and coaches, not "treaters". Passive therapies and invasive interventions are de-emphasized in favor of home exercise/self-management techniques. There should be a shift of health, function, and well-being responsibility (locus of control) from physicians and therapists to the individual. A functional restoration approach may include the limited/adjunctive use of medications and interventional measures (where specifically indicated); however, these should not be viewed as ongoing solutions, and used to support the patient's active participation in rehabilitation. Rehabilitation should

include instruction in preventive measures, education for relapse prevention, proper activity and work pacing, ergonomic accommodation, and when appropriate, recommend transitional return to employment.

The goal is a mitigation of a patient's suffering and his or her return to a productive life despite having a chronic pain problem. If an individual has risk factors for delayed recovery or fails to recover within the appropriate biological healing time frame, the acute care paradigms of specific diagnosis and treatment change to biopsychosocial approaches that address pain, function, work, and psychological factors impeding progress. Treatment programs focus on restoration of work-related function. These programs include work conditioning and work hardening, interdisciplinary pain rehabilitation programs and functional rehabilitation. Because functional restoration is an approach, not just a specific program, the approaches taken both overlap and are on a continuum.

Management Approach

Work Conditioning and Work Hardening

There is no unified agreement on definitions for work conditioning and work hardening, and sometimes the terms are used interchangeably.

Work conditioning has been defined by the American Physical Therapy Association (APTA) as "an intensive, work-related, goal-oriented conditioning program designed specifically to restore systemic neuromusculoskeletal functions (e.g., joint integrity and mobility, muscle performance (including strength, power, and endurance), motor function (motor control and motor learning), range of motion (including muscle length), and cardiovascular/pulmonary functions (e.g., aerobic capacity/endurance, circulation, and ventilation and respiration/gas exchange)."[1252]

Work hardening has been defined by APTA as a "highly structured, goal-oriented, individualized intervention program designed to return the patient/client to work. Work Hardening programs, which are multidisciplinary in nature, use real or simulated work activities designed to restore physical, behavioral, and vocational functions. Work Hardening addresses the issues of productivity, safety, physical tolerances, and worker behaviors." Thus, work conditioning is classified as a single-discipline program and work hardening program as interdisciplinary.

The Commission on Accreditation of Rehabilitation Facilities (CARF) defines occupational rehabilitation as work conditioning, and comprehensive occupational rehabilitation as work hardening. Although not universally accepted, some physicians consider work conditioning as a generalized endurance and strengthening program that includes work simulation activities, whereas work hardening is a program where a specific job has been identified and stresses involvement in sets of occupationally-related tasks and functional activities that are directly related to a patient's work. Work conditioning programs in the U.S. are most often provided by a single-therapy discipline, either physical or occupational therapy.

Early Intervention (Functional Restoration) Programs

Early identification and appropriate management of patients exhibiting signs of delayed recovery is believed to decrease the likelihood that symptoms will become chronic.[179] Patients who are identified at risk for delayed recovery may benefit from a limited but intense program of physical restoration and education, including management of barriers to recovery and return to work. These patients may require an abbreviated early

intervention interdisciplinary rehabilitation program (IPRP based on functional restoration principles, rather than a longer program utilized for more complex cases. Early intervention programs are an alternative to work conditioning and work hardening programs for subacute or early patients with chronic pain who have evidence for delayed recovery with an increased need for education and psychological assessment and intervention. These programs are usually begun when a significant gap is identified between functional abilities and job demands, ideally in the early subacute time (e.g., 30-60 days). An IPRP may also be justified earlier if risk factors for delayed recovery are identified. The interdisciplinary functional restoration program used for early intervention contains the features of a functional restoration program, but involves lower intensity and duration of services than a program used for patients with greater chronicity or intensity of disability. The type, intensity, and duration of services should be dictated by the patient's unique rehabilitation needs. These services may be used for patients who fail work conditioning and work hardening programs, usually within 6 months of onset of disability post-injury. The time frame of 3 to 6 months post-injury (or earlier if risk factors for delayed recovery are identified) is vital for intervening with the most effective treatment possible in order to avoid the negative sequelae that come with increasing duration of disability. During this time frame, normal musculoskeletal healing will generally have occurred, eliminating any remaining physical barriers to intensive rehabilitation. Such programs are appropriate for prevention, before the patient is entrenched in a chronic pain syndrome or before severe pain and illness behavior evolves.

Back Schools

Back schools are a type of secondary rehabilitation and have been used for almost 40 years for the rehabilitation of LBP patients.[1253-1255] Components of back school programs are quite variable and may include any or all of the following components: physical training, exercise, behavior modification, stress management, lifestyle change, education on anatomy, biomechanics, and "optimal posture."[1253, 1254, 1256] While the primary thrust of these programs is rehabilitation, a major secondary aim used to justify the costs of this intervention is the prevention of subsequent LBP episodes.[1255, 1257] There are different methods of program delivery including video and classroom-style presentation by a clinician.

Tertiary Pain Programs: Interdisciplinary Pain Rehabilitation Programs, Multidisciplinary Rehabilitation Programs, Chronic Pain Management Programs, and Functional Restoration Programs

There are several types of tertiary pain management programs, including interdisciplinary pain rehabilitation programs, multidisciplinary rehabilitation programs, chronic pain management program, and functional restoration programs [1258-1269]. These programs are intended to manage the psychological, social, physical, and occupational factors associated with the chronic pain problem. Precise components and emphases of these programs may vary, however, all are intended for chronic pain/disability. Most typically use a biopsychosocial approach and emphasize improved function, reduced pain and illness behaviors, and mitigation of chronic pain associated disability.

All programs generally involve an interdisciplinary team consisting of a core group of physical therapists, occupational therapists, psychologists, nurses, and case managers providing individualized treatment in a structured setting. The components offered, the sequencing of programmatic components, and the relative

importance and value of each therapeutic component frequently differ from program to program. There is also much variation in the intensity and duration of these programs.

Outcome monitoring is critical for documenting program efficacy and cost effectiveness. Multidisciplinary physician oversight is provided in such programs. Most programs include progressive physical activity, which incorporates exercise intended to move the patient toward a home fitness maintenance program and a gradual increase in personal and occupational functional tasks.

Participatory Ergonomic Programs: Return-To-Work

Participatory ergonomics are usually work-site based and generally implies that the worker is engaged in the process of job design, organization, sequencing, or layout instead of merely working on a job designed by an engineer without input into how the job is accomplished. There are two major types of participatory ergonomics teams for purposes of this discussion. One involves a proactive job design and may involve engineering, management, health care, and particularly the worker in viewing, commenting, and critiquing proposed job designs prior to implementation. This ideally also includes the potential for modifications after implementation. The other main type of participatory ergonomics involves returning a worker to a job after an injury and particularly after a prolonged absence.

Treatment Recommendations

Work Conditioning, Work Hardening, Early Intervention Programs and Back Schools for Chronic Pain

Recommended.

Work conditioning, work hardening, early intervention programs, and back schools are recommended for treatment of chronic pain patients.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – Moderate

Indications:	Patients who: 1) remain completely off work or are on modified duty for 6 to 12 weeks, most commonly due to manual materials handling tasks; 2) have not responded to less costly interventions including a 4 to 6 week physical therapy program or a graded therapy program of at least 6 to 8 weeks that includes aerobic and strengthening exercise components; 3) have a stated strong interest and expectation to return to work; 4) involve cooperation of the employer; 5) are supervised by a qualified physical or occupational therapist; 6) have had a careful assessment of their occupational demands; 7) have had either inability to return to work or a FCE that indicated appropriate performance effort and consistency at a level of work lower than that to which they need or wish to return; and 8) are in a program that includes a cognitive-behavioral approach with a focus on function rather than pain [1270], a conditioning or aerobic exercise component and simulated graded work tasks, and is tailored to their needs and identifies gaps between current capabilities and job demands. Incorporation of FABT is often helpful.
Benefits:	Improved functional recovery with faster meeting of the gap between capabilities and job demands.

Harms:	Negligible. High cost and medicalization may occur. Rare objectively worse pain condition secondary to conditioning exercises. More common is subjectively worse with exercises that usually improves or resolves with continued, but modestly reduced exercises.
Frequency/Dose/Duration:	Work conditioning and early intervention programs 3 to 5 times a week; work hardening daily. Weekly evaluations demonstrating compliance and functionally significant progress towards the return-to-work goal must be documented to justify continuation. Program length and intensity should be dictated by each patient's unique rehabilitation needs.
Indications for Discontinuation:	Program completion, return to usual work, non-compliance
Rationale:	While there is limited evidence that work conditioning, work hardening, early intervention programs and back schools are effective for chronic spinal pain, there is a longstanding belief and experience that they are highly effective. Most of the quality evidence is heterogeneous, addresses back schools, and the programmatic components are generally not well described [949, 1271, 1272] [1273] [1274-1276]. Other than use of a specific educational product, such as an educational booklet, the educational components in particular are poorly described. Descriptions of the ergonomics training are also meager, and concerning given the frequency of potentially inaccurate beliefs present.[1277] This large programmatic variability also leads to difficulties in comparing the results between many of the RCTs. Variability of quality of back schools appears to be an issue. The more successful programs appear to have greater reliance on aerobic and endurance exercises and cognitive-behavioral principles than on education or flexibility exercises. There is moderate evidence suggesting that back schools have better short-term effects than other treatments for chronic LBP and that such schools are more effective in an occupational setting than in a non-occupational setting. Select subacute LBP (towards the end of the 3-month period of subacute LBP) may be candidates, but these will occur infrequently as other treatments should be given time to prove efficacious that are also less costly. These programs are also believed to be effective for many other chronic pain syndromes, although there is no quality evidence of efficacy. While there is potential for overlap, work conditioning, work hardening, early intervention (see below) and back schools are distinct programs and are not intended for sequential use, although this may be appropriate in certain situations depending on program components. In acute cases, where delayed recovery is not an issue, these programs are inappropriate. In subacute pain, there may be highly limited applicability, particularly if there is an early identification that the primary obstacle to RTW is inability to accomplish the job demands. In more chronic cases, particularly with pain and illness behavior and a high level of reported dysfunction, a more intense IPRP should be considered. Although less costly, work conditioning, work-hardening and early intervention programs do not need to be attempted before moving to an IPRP as long as a quality interdisciplinary program with proven outcomes is accessible to the patient. Program choice depends on availability and matching patient needs to the services offered to provide the most cost-effective and beneficial outcome. Hence, these programs may provide the greatest potential impact when used to manage patients during the subacute phases of injury, although they may also be appropriate for use in those with chronic pain who do not, after evaluation, have significant

psychosocial factors contributing to their clinical presentation. These programs are not invasive and have low adverse effects, but are moderate to high cost depending on program length and are selectively recommended.

Evidence:

Work Conditioning, Hardening, Early Intervention – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: work conditioning, hardening, early intervention; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 15 articles in PubMed, 36 in Scopus, 4 in CINAHL, 66 in Cochrane Library, 17600 in Google Scholar, and 0 from other sources. We considered for inclusion 1 from PubMed, 2 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 0 from Google Scholar, and 2 from other sources. Of the 5 articles considered for inclusion, 3 randomized trials and 2 systematic studies met the inclusion criteria.

Back Schools – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: back schools; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 62 articles in PubMed, 98 in Scopus, 14 in CINAHL, 8 in Cochrane Library, 200,000 in Google Scholar. We considered for inclusion 20 from PubMed, 11 from Scopus, 0 from CINAHL, 3 from Cochrane Library, 4 from Google Scholar, and 33 from other sources. Of the 71 articles considered for inclusion, 46 randomized trials and 25 systematic studies met the inclusion criteria.

There is 1 high-quality [1270] study and many moderate studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4. There are also a few case series [1281-1284].

Tertiary Pain Programs: Interdisciplinary Pain Rehabilitation Programs, Multidisciplinary Rehabilitation Programs, Chronic Pain Management Programs, and Functional Restoration Programs

Recommended.

Tertiary Pain Programs, including interdisciplinary pain rehabilitation programs, multidisciplinary rehabilitation programs, chronic pain management program, and functional restoration programs are selectively recommended for patients with chronic pain who have failed conventional treatments and remain significantly incapacitated.

Strength of Evidence – **Recommended, Evidence (C)Recommended, Evidence (C)**
Level of Confidence – Low

Indications:

The most important tertiary pain program criterion is a proven track record of positive outcomes relevant to overcoming disability without excess health care utilization. The programs with favorable outcomes tend to be those that emphasize principles of functional restoration. There is great variability in the

quality of care in these programs, and familiarity with a program and its "track record" may be necessary before referring a patient for a specific program. It is important to assess whether the patient has failed prior rehabilitation within the same facility or other similar programs, or whether conflicts of interest are involved in referral to the tertiary pain program facility.

Prior to beginning a tertiary pain program, a patient must go through a thorough evaluation which should comprise a record review and assessment by program personnel including a pain physician, a medical history and physical, a comprehensive evaluation by a psychologist, and an evaluation by a therapist (PT and/or OT). The purpose of these assessments is to rule out treatable conditions, identify addiction issues (and refer elsewhere if needed), and establish patient appropriateness for a tertiary pain program. These evaluations also should identify barriers to recovery that will need to be dealt with by the treatment team during the program, including fear avoidance beliefs ("kinesiophobia"), fear of re-injury, and potential barriers to physical progress and assessment. The PT/OT evaluation usually includes baseline functional abilities testing to quantify capabilities. The baseline PT/OT evaluation may include a full FCE. Other evaluations (e.g., case management or nursing assessments) are done if additional information is necessary to specifically assess patient benefit and to help guide the treatment in the program.

The decision to admit the patient to a tertiary pain program should be based on all of the following criteria:

1. Patients are either completely off work or on modified duty for at least 3 months and trending towards unusually slow and delayed functional recovery
2. There is a known etiology to the chronic pain syndrome or specific clinical condition which includes physical injury or disease.
3. Other appropriate medical and/or invasive care has been attempted and proved to be inadequate to restore functional status.
4. The patient has appropriate rehabilitation potential (i.e., he or she is judged to be able to substantially benefit from the program).
5. The patient is not responding to less costly interventions including quality physical therapy programs;
6. The patient has at least some behavioral or psychosocial issues affecting their recovery. For workers without behaviorally related issues and merely a physical gap between the current capabilities and future job requirements, work conditioning/work hardening programs are usually both more appropriate and cost effective.
7. The patient has substantial gaps between current physical capabilities and actual or projected occupational demands
8. There are no known contraindications to the treatment program, e.g., certain unstable medical conditions, primary substance abuse disorder or cognitive limitation which would prevent appropriate learning.
9. The patient is committed to recovery.

There is no specific timeframe which is required to elapse before attempting a tertiary pain program. Some patients demonstrate a chronic pain syndrome with significant disability within a few weeks of injury. For others, 6 months or more may elapse before chronic pain syndrome changes occur and/or the above conditions are met. At this time, there is no quality evidence that a full tertiary pain program is necessary to *prevent* the evolution of a chronic pain syndrome. Success in this regard is based on appropriate medical and functionally based care [1270].

All tertiary pain programs involve an integrated team of professionals who provide intensive, coordinated care. This team may include physical and occupational therapists, psychologists, vocational counselors, nurses, and case managers. Incorporation of FABT often helpful. All medical and therapy services must be supervised by a physician who is directly involved with the program and regularly interviews and examines the patient for relevant parameters.

A special consideration applies to patients with significant opioids and/or benzodiazepine and/or addictive substance(s) use. These patients may require significant involvement of an addiction specialist for success of a tertiary interdisciplinary or multi-disciplinary pain treatment program for that particular patient. In some cases, detoxification and/or treatment by an addiction specialist may be necessary before consideration of treatment by an inter- or multidisciplinary pain program.

Benefits: Improvement in function, return to work, return to unrestricted duty. Improved functioning in home, work and community settings. May facilitate opioid weaning process.

Harms: High costs. Further medicalization. Some pain programs do not primarily concentrate on functional recovery and prescribe excessive opioids and excessive interventional techniques which are avoidable through proper referrals.

Frequency/Dose/Duration: Progressive physical activity, which incorporates exercise intended to move the patient toward a home fitness maintenance program and a gradual increase in personal and occupational functional tasks. Tertiary pain program treatment is generally 5 full days a week. Treatment program length is determined by the severity of deficits, speed of progress, cessation of healing (or reaching a "plateau"), and thus are somewhat individualized. Typical lengths are 4 to 6 weeks. Complicating problems such as coordinating with part-time work, transportation, child care, extreme physical deficits, high-dose opioids, or limitations imposed by comorbid medical conditions are considerations that may necessitate a slower approach to program participation and longer treatment duration.

In most effective tertiary pain programs, physical reconditioning, patient education, behavior modification, fear avoidance ("kinesiophobia"), stress management or biofeedback procedures, and treatment of patients in groups (in part) are also key components. Regular monitoring of progress, modification of treatment plans, and interdisciplinary team communications are required. Outcome monitoring is critical for documenting program effectiveness. Patient

access to programs with demonstrable relevant outcomes is essential for treatment efficacy. The effectiveness of these programs has been documented and they are cost-effective with respect to direct health care expenditures, disability costs, and other economic indicators.[75, 1337, 1338]

Treatment Objectives. Appropriate treatment objectives must include the following which have to be regularly assessed and documented:

1. *Functional improvement.* This should emphasize those physical parameters which have been assessed as "pain limited." (Kool 05) While general or aerobic conditioning is appropriate for most patients, there should be evidence of progress in the specific areas where dysfunction or deficits have been present.
2. *Improvement in activities of daily living.* These are unique to each patient and goals should also be relevant to "pain limited" activities.
3. *Relevant psychosocial improvements.* Objective improvement in patient's psychosocial functioning should be evident.
4. *Withdrawal from opioid, sedative-hypnotic, and muscle relaxant medications.* This is a requirement, absent specific indications. A history of adequate functional improvement associated with opioid medications would not by itself result in referral to a tertiary pain program unless excessively high doses of medications are being used with associated physical and psychological dysfunction.
5. *Medical management.* All other medications should be continually reviewed and adjusted as necessary.
6. *Return to work or other productive activity.* Appropriate assessment, counseling, planning, and skill development should begin early in the program with efforts directed at identifying if it is reasonable for the patient to return to work.

Inpatient Care. Nearly all patients can be treated on an ambulatory basis. In the rare circumstances where hospitalization is required, this should be under the control of or closely coordinated with a tertiary pain program physician. Indications for inpatient care include any of the following:

1. detoxification on an outpatient basis may present unacceptable medical risk;
2. medical instability;
3. the evaluation suggests that treatment may exacerbate pain/illness behavior to the extent that there is a risk of injury or render florid manifestation of a major psychiatric disorder;
4. 24-hour nursing care is required;
5. extreme pain behavior and dysfunction that makes outpatient care not feasible and there is reasonable evidence presented by the evaluating pain team that a brief inpatient stay will enable transfer to an outpatient tertiary pain program.

When these conditions no longer apply, the patient should be discharged.

Non-indicated Therapies. Therapies such as injections which do not have specific indications have the distinct potential to reinforce pain/illness behavior

and therefore retard functional progress in a tertiary pain program. There is no evidence that such procedures provide any incremental benefit in a tertiary pain program. There is also no empirical evidence that passive modalities (e.g., heat, cold, ultrasound, massage) provide additional benefit in a tertiary pain program. These should only be used for specific, limited indications and if they facilitate improvement in exercise or function.

Other Functional Restoration. At times, patients may require functional restoration, but find that either a formal program does not exist or it is not appropriate due to medical or social issues. In such cases, functional restoration can sometimes be accomplished, provided the patient requires treatment for specific clinical indications with the services which are to be provided. At a minimum, there should be appropriate indications for behavioral/psychological treatment, physical or occupational therapy, and at least one other rehabilitation oriented discipline. Care must be coordinated by a physician appropriately qualified and experienced to provide and supervise rehabilitation services or functional restoration. Criteria for the provision of such services should include:

1. Satisfaction of the criteria for coordinated functional restoration care as appropriate to the case;
2. A level of disability or dysfunction which does not *require* treatment in a formal program;
3. No drug dependence or problematic or significant opioid usage; and
4. A clinical problem for which return to work can be anticipated upon completion of the services.

Follow-up. Regular or intensive formal treatment is not usually necessary after successful discharge from a tertiary pain program. However, it is important that patients continue a self-directed home program of physical restorative and psychological pain management approaches learned during the tertiary pain program. Routine follow-up should be provided to assess the durability of the functional restoration achieved, with a long-term-care plan established to facilitate management by the treating physician.

Indications for Discontinuation: Program completion or non-compliance. When appropriate progress is not achieved, the tertiary pain program should be terminated. However, for many patients notable progress may not be achieved in the early stages of a program; some may briefly, initially worsen with respect to certain program goals.

Rationale: There are several studies of various tertiary pain programs to treat musculoskeletal disorders and the literature is fairly heterogeneous, although favorable data have been published. [1270, 1339, 1340] [1341-1350] With the possible exception of the workplace-based interventions, most successful multidisciplinary programs appear to have either utilized a cognitive-behavioral approach or involved psychologists.[1351-1354] Similar to the literature, the programs available are also highly heterogeneous making comparisons between programs difficult. The programs in the literature could be mostly segregated into two basic types: 1) a program consisting of a limited number of disciplines in a combined behavioral-exercise approach (e.g., an occupational physician,

physiotherapist, and psychologist); and 2) a workplace focused program to facilitate return to work with a multidisciplinary, participatory ergonomics team approach (ergonomist, worker, supervisor, and others). There is a near total absence of quality studies that assess multidisciplinary programs that include interventional approaches as are common in the U.S. In addition, the preponderance of the evidence is based on patients with LBP.[1270] Other conditions have not been systematically studied. Participation in a tertiary pain program has only been reported in one study of upper extremity MSDs (which may have issues of diagnostic and interventional considerations) and was not shown to be of benefit.[1355] These programs may be particularly helpful if there is medical need to wean the patient from opioids or other medications and/or the patient has shown demonstrable clinical progress with less intense rehabilitation but that "pain limitation" has impeded adequate recovery. Development of entrenched psychosocial barriers to recovery and a chronic pain syndrome as sequelae of the original physical components of the injury may be associated with this group of patients. Functional restoration may be appropriate, as well as vocational re-entry in positions not requiring the same job physical characteristics when all previous treatments have failed.

With the possible exception of workplace-based interventions, most successful multidisciplinary programs appear to have either utilized a cognitive-behavioral approach or involved psychologists.[1352, 1354, 1356, 1357] While exercise is a major focus in a number of these successful programs,[1315, 1352, 1354, 1356, 1357] the one trial comparing a graded exercise approach with a participatory ergonomics approach found exercise was inferior.[1358] This suggests that of the various options available, the participatory ergonomics approach may be superior to other approaches.[1359] These heterogeneous studies also suggest that multidisciplinary programs that focus on functional improvements are superior [1270]. These programs have also been shown to be as effective as spinal fusion surgery.[31, 33, 1356]

Some U.S.-based programs involve significant interventions, but there is no documentation of superior outcomes from such programs which can be expensive (>$20,000 to $50,000). Tertiary pain programs are indicated for select, more severely affected patients, including those who have failed appropriate conservative management (e.g., appropriate medications, specific exercises, etc.). Generally, these referrals are most indicated in the early chronic pain management timeframe (3 to 6 months). However, there are times when earlier referral in the mid- to late-subacute interval is indicated. (One should be aware that there is a belief that earlier referral results in higher probability of successful treatment, but that supposition has not been rigorously tested and is prone to a strong spectrum bias whereby all patients tend to do worse the longer they have the acute, subacute, or chronic pain condition.) Referrals beyond 6 months may also be indicated if there has been failure to progress with numerous interventions and there is reasonable expectation for potential benefits. Referrals during the subacute phase best occur when there is a quality program with proven outcome efficacy available, the patient has documented delayed recovery, yet there is interdisciplinary assessment that the patient is likely to

benefit from the program. Tertiary pain programs of the types described in the literature are not invasive, have few adverse effects, but are high cost. They are selectively recommended for highly select patients.

Evidence:

Interdisciplinary Pain Rehabilitation – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Interdisciplinary Pain Rehabilitation, Interdisciplinary Pain Rehabilitation Program; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 154 articles in PubMed, 100 in Scopus, 17 in CINAHL, 92 in Cochrane Library, 8,400 in Google Scholar, and 11 from other sources. We considered for inclusion 5 from PubMed, 4 from Scopus, 2 from CINAHL, 1 from Cochrane Library, 2 from Google Scholar, and 11 from other sources. Of the 25 articles considered for inclusion, 13 randomized trials and 2 systematic studies met the inclusion criteria.

Multidisciplinary Rehabilitation – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: multidisciplinary work rehabilitation program, multidisciplinary work rehabilitation, work rehabilitation, multidisciplinary rehabilitation, multidisciplinary pain program; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 599 articles in PubMed, 302 in Scopus, 81 in CINAHL, 361 in Cochrane Library, 17,000 in Google Scholar, and 27 from other sources. We considered for inclusion 14 from PubMed, 3 from Scopus, 4 from CINAHL, 4 from Cochrane Library, 0 from Google Scholar, and 27 from other sources. Of the 53 articles considered for inclusion, 47 randomized trials and 4 systematic studies met the inclusion criteria.

Chronic Pain Management Program/ Functional Restoration Program – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Chronic Pain Management Program, Functional Restoration Program, Chronic Pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 97 articles in PubMed, 5382 in Scopus, in 16 CINAHL, 19 in Cochrane Library, 34200 in Google Scholar, and 0 from other sources. We considered for inclusion 13 from PubMed, 0 from Scopus, 4 from CINAHL, 2 from Cochrane Library, 6 from Google Scholar, and 0 from other sources. Of the 25 articles considered for inclusion, 18 randomized trials and 4 systematic studies met the inclusion criteria.

Functional Restoration – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: functional restoration pain program, functional

rehabilitation therapy; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 1,087 articles in PubMed, 287 in Scopus, 11 in CINAHL, 824 in Cochrane Library, 18,800 in Google Scholar, and 1 from other sources. We considered for inclusion 29 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 7 from Google Scholar, and 0 from other sources. Of the 38 articles considered for inclusion, 25 randomized trials and 7 systematic studies met the inclusion criteria.
There are high-quality and moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Participatory Ergonomics Programs for Patients with Chronic Pain

Recommended.

Participatory ergonomics programs are recommended for select patients with subacute and chronic pain.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – Moderate

Indications:	Patients with subacute and chronic pain who remain off work or on a different job, have apparent workplace barriers to return to work, and where there is managerial support and interest in analyzing and addressing barriers. This may be particularly beneficial in settings with low or no effective controls on lost time. Primary preventive programs may be best indicated in high-risk jobs, especially those with high-force requirements.
Benefits:	Earlier return to work. Primary, secondary, and tertiary prevention. Improved and earlier functional recovery through earlier return to work.
Harms:	Negligible. Risk of managerial attention to a worker with subsequent workplace labeling of a 'problem worker.'
Frequency/Dose/Duration:	Generally only one evaluation of a job and workplace is needed. A second evaluation of potential interventions may occasionally be needed.
Indications for Discontinuation:	Workplace is unable to change the job, infeasibility, noncompliance, disinterest.
Rationale:	Quality evidence is available to assess the effects of a participatory ergonomics return to work program for subacute to chronic LBP. However, studies have largely been performed in Europe where practices are far different, lost time may be more extensive and therefore, generalizability to the U.S. is unclear [1393-1395]. In addition, the return to work timeframe has likely shifted in the US to far earlier timeframes than in the past as the concept of "rest" for back pain has been shown to be unhelpful. Return-to-work programs may be low cost relative to the lost time saved particularly where there are no other controls on lost time. These programs are not invasive and have low potential for adverse effects. However, they do require willingness and interest among multiple parties to be successful.
Evidence:	*Participatory Ergonomics* – A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without

date limits using the following terms: Participatory Ergonomic, participatory ergonomics; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 4 articles in PubMed, 0 in Scopus, 0 in CINAHL, 1 in Cochrane Library, 252 in Google Scholar, and 10 from other sources. We considered for inclusion 1 from PubMed, 0 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 1 from Google Scholar, and 10 from other sources. Of the 11 articles considered for inclusion, 10 randomized trials and 1 systematic studies met the inclusion criteria.

There are moderate-quality studies incorporated into this analysis. There is low-quality evidence listed in Appendix 4.

Treatment Evidence

Evidence for Work Conditioning, Work Hardening, and Early Intervention Programs

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow Up Duration:*	*Results:*	*Conclusion:*	*Comments:*
Sundstrup, 2014 (score=6.0)	Working Conditioning, Hardening, Early Intervention	RCT	Supported by a grant from the Danish Parliament and Danish Working Environment Research Fund. No COI.	N = 66 patients with chronic pain in shoulder, elbow/forearm or hand/wrist.	Mean age: 45.5; Sex: 51 males, and 15 females.	Resistance Training (RT) group received 10 weeks of resistance training in order to increase physical capacity on pain and disability. (N =33) vs Ergonomic Training (ET) group received ergonomic training and education based on practical outcomes of worksite analysis. (N=33)	10 weeks	Group differences (RT vs EG): Average pain intensity (-1.5, ($p<0.001$)), DASH-W score (-8.8 ($p<0.05$)), Shoulder Rotation Strength (37, ($p<0.001$)), Wrist Extensor Strength (42, ($p<0.001$)).	”Resistance training at the workplace results in clinical relevant improvements in pain, disability, and muscle strength in adults with upper limb chronic pain exposed to highly repetitive and forceful manual work.”	Usual care bias. Data suggest resistance training is advantageous for reducing pain and disability and improving muscle strength for manual workers who perform repetitive and force related tasks.

Hlobil, 2005 (score=6.5)	Work conditioning, work hardening, early intervention program	RCT	Support was by the Dutch Health Insurance Executive Council (CVZ), grant no. DPZ 169/0. No mention of COI.	N = 134 KLM airline workers on site at Schiphol Airport	Mean age: 38 years; 126 males, 8 females.	Usual treatment (n = 67) vs. graded exercise program (n = 67). Intervention 60-minute exercise sessions 2 times a week up to 3 months	6 months	Median lost time after intervention in interventional group 54 vs. 67 days in usual care group. Hazard ratio from 50 day after randomization and onwards favored graded exercise group, p = 0.01. Hazard ratio from 50 days onwards favored graded exercise, p <0.01. NS between groups for total days of sick leave due to recurrent episodes of LBP during 12 month follow-up.	"Graded activity intervention is a valuable strategy to enhance short-term return to work outcomes."	Program had less exercise time than typical in U.S., thus benefits may be underestimated. Noteworthy that at this time, "completing 365 sick leave days entitled the worker to receive disability benefits," thus providing governmental, policy bias against success of program. Demographic information not provided.
Li, 2006 (score=6.5)	Work conditioning, work hardening, early intervention program	RCT	No industry sponsorship or COI.	N = 64 with musculo-skeletal injury and long-term sick leave	Mean age: 43.97 years; 40 males, 24 females.	3-week training on work readiness (n = 34) vs. advice on employment placement (n = 30).	3 weeks	MB knees had larger incremental increase in tibial internal rotation than FB 4.3°, 7.5°, 9.5° vs. 3.0°, 3.0°, 4.2° respectively (at 30, 60, and 90 degrees). 90° difference significant (p = 0.043).	"[T]raining on work readiness program appeared to be effective in reducing the anxiety and stress levels of the injured workers, improving their self-perception of health conditions, thus gradually	Function comparable but less radiolucency at 2 years with mobile bearing. Demographic information not provided.

								Incidence of radiolucent lines at tibia implant interface higher in FB knee (p = 0.005). Knee society, WOMAC, and sf-36 scores increased in both groups but did not differ from each other significantly in any area.	creating behavioral changes on their work readiness."	

Evidence for Interdisciplinary Work Rehabilitation Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow -up:	Results:	Conclusion:	Comments:
Staal 2004 (score=8.5)	Interdisciplinary work Rehabilitation program	RCT	Supported by Dutch Health Insurance Executive Council. No COIs.	N = 105 with subacute LBP (median 8 to 8.5 weeks duration, range 6 to 14 weeks) among airline employees	Mean age: 38; Sex: 126 males, 8 females.	Behavioral-oriented, graded exercise therapy (n = 67) vs. Highly heterogeneous group of usual care methods (n = 38 physiotherapy, n = 6 manual therapy, n = 6 Mensendieck exercise therapy, n = 3 chiropractor, n = 1 back school, n = 7 unknown). Intervention group with 2x a week-1 hour exercise sessions with physiotherapists emphasizing operant conditioning,	6 months	At 6 months, pain ratings not different, but improved more in graded exercise group (3 months/6 months: 2.8 2.4/2.9±3.1 vs. 2.5±2.8/2.7±2.8, p >0.2). Over 6 months of follow-up, median lost time 58 vs. 87 days.	"Graded activity was more effective than usual care in reducing the number of days of absence from work because of low back pain."	Despite high-quality score on grading, due to inclusion of multiple research study design techniques, study so heterogeneous that firm conclusions are not warranted for any single intervention.

						focusing on achieving goals to improve function. Sessions until RTW or 3 months.				
Hlobil 2005 (score=6.5)	Interdisciplinary work Rehabilitation program	RCT	Supported by Dutch Health Insurance Executive Council. No COIs were mentioned.	N = 134 workers for KLM airline workers onsite at Schiphol Airport	Mean age: 38; Sex: 126 males, 8 females.	Usual treatment (n = 67) vs. graded exercise program (n = 67). Intervention 60-minute exercise sessions 2 times a week for up to 3 months.	6 months	Median lost time after intervention in interventional group was 54 vs. 67 days usual care group. Hazard ratio for period from 50 days after randomization onwards favored graded exercise group, p = 0.01. Hazard ratio from 50 days onwards favored graded exercise group, p <0.01. NS between groups for total days sick leave due to recurrent episodes of LBP during 12 month follow-up period.	"Graded activity intervention is a valuable strategy to enhance short-term return to work outcomes."	Program had less exercise time than typical U.S.-based program, thus benefits may be an underestimate. It is also noteworthy that at this time, "completing 365 sick leave days entitled the worker to receive disability benefits," thus providing governmental, advocagenic policy bias against success of this program.
Moffett 1999 (score=6.0)	Interdisciplinary work Rehabilitation program	RCT	Supported by grant from Arthritis Research Campaign, Northern and Yorkshire	N = 187 with subacute and chronic LBP	Mean age: 41.8; Sex: 81 males,	Graded exercise (n = 85, program of 8 exercise classes) vs. Routine general practitioner	6 & 12 months	Roland Disability scores in controls and exercise groups reduced at 6 months (-1.64 and -2.99 respectively, p	"Our exercise programme did not seem to influence the intensity of pain but did affect the participants' ability to	Trial uses usual care as control, which may be biased against that

			Regional Health Authority, and National Back Pain Association. No COIs.		106 females	management (n = 98).		= 0.03) and 1 year (-1.77 and -3.19, respectively, p = 0.02) compared to baseline. There were 378 lost workdays in intervention group vs. 607 in controls.	cope with the pain in the short term and even more so in the longer term. It used a cognitive-behavioral model…and with minimal extra training a physiotherapist can run it. Patients' preferences did not seem to influence the outcome."	arm. Treatments in usual care also not standardized and may not represent modern practice. Total costs 50% greater in controls, with cost differences mostly due to lost time. Data suggest graded exercise program superior to usual care.
Li 2006 (score=6.5)	Interdisciplinary work Rehabilitation program	RCT	No mention of COIs or industry sponsorship.	N = 64 with musculoskeletal injury and long-term sick leave	Mean age: 43.9; Sex: 63 males, 40 females.	3-week training on work readiness (n = 34) vs. Advice on employment placement (n = 30).	3 weeks	Subjects in training group showed significant improvement in work readiness (p <0.05), level of anxiety (p <0.05) and self-perception of health status measured by SF-36 (p <0.02) vs. control group. Control of chronic pain, negative motivation, anxiety level some of key behavioral changes found from study.	"[T]raining on work readiness program appeared to be effective in reducing the anxiety and stress levels of the injured workers, improving their self perception of health conditions, thus gradually creating behavioral changes on their work readiness."	Small sample size.
Johnson 2007 (score=6.0)	Interdisciplinary work	RCT	No COIs or industry sponsorship	N = 234 with persistent disabling LBP of over 3	Mean age: 47.9;	Active exercise, education and CBT 2-hour group sessions over 6-week period	Follow at 3, 9, 15	Patients who preferred intervention and assigned to it experienced	"This intervention program produces only modest effects in reducing LBP and	Study reviewed in psychological section as it

	Rehabilitation program			months duration at enrollment	Sex: 94 males, 140 females.	(n = 116) vs. Control treatment (n = 118).	months	significant reductions in pain and disability scores. Those preferring controls had worse outcomes. Those with no preference, little intervention effects. No differences between groups over 15 months of follow-up.	disability over a 1-year period. The observation that patient preference for treatment influences outcome warrants further investigation."	does not appear to rely primarily on exercise for treatment. Compliance 63% intervention group. No significant effect found. Other co-interventions not well described.
Van Der Maas, 2015 (Score=4.0)	Interdisciplinary Work Rehabilitation Programs	RCT	No mention of sponsorship. No COI.	N=94 patients with chronic pain.	Mean age: 41.86 years; 17 males, 77 females.	Treatment as Usual (TAU) group: relaxation (6 X 1.5 h), aerobic fitness (33 X 1 h), rational-emotive therapy (9 X 1h, 6 X 1.5h) occupational therapy (6 X 1.5), chronic pain education (3 X 1.5h), sports (in the swimming pool [5 x 1 h] and in the sports hall [5 X 1 h]), partner education (3 X 1.5 h), and coaching (4 X 1 h), a total of 94 hours (n = 45) vs Treatment as usual with Psychomotor Therapy (PMT): (10 X 1.5) body experience and interaction and communication focus. (n = 49)	3, 6, and 12 months	TAU vs PMT Pain intensity; 5.78 vs 5.51 (p = 0.459). PDI overall time effect -1.58 vs -1.83 RAND-36 PCS .25 vs 0.96 RAND_36, MCS 1.49 vs 1.04 BDI -1.04 vs -1.54 SBCBA .04 vs 0.11 PSEQ 1.20 vs 1.27. PMT differed from TAU on depression (RC=-5.01, 95% CI -8.81 to -1.21), body awareness [RC=0.23, 95% CI 0.04 to 0.42), and catastrophizing (RC=-4.76, 95% CI -8.03 to -1.48).	"No clinical meaningful differences were found between treatment conditions in the primary outcome measures health related, quality of life and disability."	Difference in contact time between groups. High dropout rate at 12 months. Data suggest similar efficacy in clinical outcomes PMT group had significantly less depression and catastrophizing as well as improvement in BA.

Rothman, 2012 (score=4.0)	Interdisciplinary Work Rehabilitation Programs	RCT	No mention of sponsorship. No COI	N=182 Patients with chronic musculoskeletal pain	Mean age: 40 years; 43 males, 139 females,.	Multimodal assessment (MM): Multidisciplinary group therapy, individual multidisciplinary therapy, referral back for conventional treatment. (n=91) vs Conventional multidisciplinary and unimodal assessment (CMUA): conventional multidisciplinary pain management or unidisciplinary treatment (n=91)	15 months	MM baseline vs 15mo Pain vas 69.5 vs 60 (p = 0.002) stress 60 vs 56 (p = 0.067) ODI 40 vs 36 (p = 0.017) Control baseline vs 15mo pain VAS 74.5 vs 65.5 (p = 0.008) stress 54.5 vs 51 (p = 0.673) ODI 38 vs 38 (p = 0.686).	"The patients receiving the MM assessment improved their QOL and working ability, and were also significantly more satisfied with the assessment they received. However, there were no differences between groups regarding a patient's pain intensity, depression, stress symptoms, or disability levels at the 15-month follow-up. Pretreatment MM assessment is, therefore, an option to be used to select and prepare patients for the most suitable subsequent rehabilitation treatment and could be used in a primary care setting. A pretreatment MM assessment for patients with mixed CMP is, thus, recommended."	80% of patients female. Routine care control bias. Data suggest improved satisfaction in MM assessment group.

Evidence for Back Schools

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ribeiro, 2008 (score=5.5)	Rehabilitation for delayed recovery	RCT	No mention of sponsorship. No COI.	N = 60 with cLBP.	Mean age: 50.45 years; 10 males, 45 females.	Intervention group (IG, N = 29): back school with anatomy ergonomics, ab and back strengthening, and relaxation postures for 1 h/week for 4 weeks, and 1 h session at 30 days vs Control group (CG, N = 31): 3 medical check-up visits with a rheumatologist over 4 weeks, and once 30 days later. Both groups received analgesic medication and acetaminophen.	Follow-up at baseline, 30, 60, and 120 days.	Acetaminophen intake for IG at day 30 (p=0.039), and a difference between groups at day 120 with less intake for IG (p=0.046). All areas of the SF-36 domain did not have significant results except for improvement the general health domain for IG (p=0.018). There were no statistically significant results between groups in VAS scores (p=0.601), Rolland-Morris questionnaire (p=0.735), Schober's Test (spine mobility, p=0.983), and Beck Depression Inventory (traits p=0.697, anxiety p=0.706).	"The results of the present study demonstrate the limited effectiveness of the back school program in the management of chronic nonspecific low back pain when compared to medical visits without educational intervention."	Data suggest comparable efficacy between groups for pain, functional status, anxiety and depression but the back school program appeared to decrease acetaminophen and NSAID consumption.
Morone, 2011 (score=5.5)	Back School	RCT	No mention of industry sponsorship or COI.	N = 73 with chronic non-specific LBP	Mean age of BSG group: 61.2, CG group: 58.6.	Treatment group received intensive multidisciplinary back school program including brief	Follow-up at 3 and 6 months.	Treatment group favored in Waddell Disability Index (WI) at 3 months (p = 0.006) and 6 months (p = 0.009). ODI also similar at 3 months (p = 0.018)	"Our Back School program can be considered an effective treatment in people with chronic non-specific LBP."	Higher baseline ODI in Back School. 1hr sessions for Back School is low for most programs. Baseline

					Sex(M:F) 25:45	education and active back exercises (n = 41) vs Control group received medical assistance (n = 29).		and at 6 months (p = 0.011). Both groups improved significantly in VAS scores, but treatment group favored at end of treatment (p <0.001), at 3 months (p <0.001), and at 6 months (p <0.001).		differences limit interpretation as does control group as equivalent to a wait-list control bias.
Paolucci, 2012 (score=5.5)	Back School	RCT	No mention of industry sponsorship or COI.	N = 50 with chronic non-specific LBP	Mean age of Back school group: 59, Control group: 57.25. Sex(M:F) 19:31	Treatment group received intensive multi-disciplinary back school program including brief education and active back exercises (n = 21) vs. Control group received medical assistance (n = 29).	Follow-up at 3 and 6 months.	Treatment subgroups only groups to show significant improvement in quality of life. Similar results seen in terms of WI, ODI, and VAS for treatment subgroups.	"[P]atients with chronic non-specific low back pain presenting elevation of one or more scale scores of MMPI-II may benefit by specific educational exercises, such as Back School Program, similarly to other patients in terms of physical improvement and even more in terms of mental improvement."	Secondary analysis to Morone 2011.
Jaromi, 2012 (score=4.5)	Rehabilitation for delayed recovery	RCT	No mention of sponsorship or COI.	N = 124 nurses with CLBP	Mean age: 31.9 years; 18 males, 93 females.	Intervention group: ergonomics training and back school (ergonomics training exercise and muscle strengthening and stretching) for 50 min sessions 1x/w	Follow-up at 6 and 12 months.	LBP intensity from pre to post-therapy (p=0.000). The intervention group at 6 and 12 months compared to pre-therapy (p=0.000) in reduced LBP intensity. There were also significant results only for the intervention group	"The data from the current study showed that for the group who participated in the BS programme, and thus received education and ergonomics skills, the body posture improved, pain was significantly	Time of exercise therapy per week dissimilar between groups. Data suggest significant improvement in pain intensity in both groups but at both 6-months and 1-

						for 6 weeks, and to continue exercises at home during the week (N = 56) vs Control group: passive physiotherapy (TENS and heat therapy, ultrasound and Swedish massage on lumbosacral region) 1x/w for 6 weeks (N = 55).		at post-therapy, 6 month, and 12 month follow-up compared to pre-therapy for body posture in thoracic kyphosis angle, and lumbar lordosis angle (p=0.000 for each).	decreased in post-therapy and at the long term at the followup visits as well."	year following the BS group shoved improved pain and posture over control group.
Paolucci, 2016 (score=4.5)	Rehabilitation for delayed recovery	RCT	No COI. No mention of sponsorship.	N = 53 with a diagnosis of chronic low back pain.	Mean age: 60.96 years; 11 males, 42 females.	Feldenkrais group (N = 26) vs Back School group BS (N = 27),	3 - months	At the end of treatment (Tend), between groups regarding chronic pain reduction (p=0.290); VAS and MAIA-N sub scores correlated at Tend (R=0.296, p=0.037). By the Friedman analysis, changes in pain (p<0.001) and disability (p<0.001) along the investigated period.	"The efficacy of the Feldenkrais method was comparable with that of the BS for nonspecific CLBP."	Data suggest comparable efficacy.
Constantino, 2014 (score=4.5)	Rehabilitation for delayed recovery	RCT	No mention of sponsorship or COI.	N = 56 with chronic NSLBP.	Mean age: 73.46 years; 30 males, 24 females.	Back school program: education on anatomy, ergonomic positions, psychological management,	Follow-up at baseline (T0), 12 (T1), and 26 weeks (T2).	Statistically significant results were seen from T0 to T1 in improvement in RMDQ and SF-36 scores for both Back School (p<0.001,	"[T]he lack of significant difference between the two programs highlighted by the data proved that both therapeutic	Comparable efficacy between groups.

						and muscle strengthening and stretching (N = 28), vs Hydrotherapy program: pool exercises of strengthening and stretching (N = 28). Each group had 1 hour treatment sessions 2x/w for 12 weeks.		p<0.001 respectively), and Hydrotherapy (p<0.001, p<0.001 respectively). The same significant results were seen from T0 to T2 in both groups. There were no statistically significant difference between the two groups at T0, T1, and T2 (p=0.096, p=0.925, p=0.885 respectively).	options could be equally effective in treating CLPB in elderly people".	
Henchoz, 2010 (score=4.0)	Back School	RCT	No mention of industry sponsorship or COI.	N = 109 with subacute (> 6 weeks) or chronic (> 12 weeks) LBP	Mean age: 39.6; Sex: 69 males, 33 females.	Functional multi-disciplinary (FMR) (n = 56) vs Outpatient physiotherapy (OP) (n = 23).	12 months	At 12 months the FMR improved significantly compared to OP in work status (p = 0.012). Fingertip-floor distance was also significantly improved in the FMR group compared to OP at 12 months (p = 0.037). There were no other significant findings between groups at 12 months follow-up.	"[T]he FMR group evolved significantly more favorably compared to the OP group in disability in the short and long terms, and in work status at long term."	Much missing data, especially OP group. Baseline differences including better fitness in MDRP group, possible moderate randomization failure. As all of work <6mo, likely had PT, which would bias in favor of other treatment. Data favor MDRP.
Durmus, 2014 (score=4.0)	Rehabilitation for delayed recovery	RCT	No mention of sponsorship. No COI.	N = 127 with CLBP	Mean age: 53.06 years; 0 males, 121 females.	Group 1: exercise treatment (flexibility and strengthening, N = 63), vs Group 2: low back	Follow-up at baseline (BT), 3 (AT) and 6 months (F).	Group 1 from BT to AT, and BT to F in ODQ, 6MWT, VAS pain, FMS, EMS, AET, QMS (right and left), EET, Beck depression score,	"The results of this study showed greater improvements in pain, disability, trunk and knee muscle strength, walking	Both groups showed significant improvement but mobility improved more in the combined back school

						school (ergonomics, anatomy, functional ADL movement and rest) and exercise treatment (N = 64). Both groups had 60 min of exercise therapy 3x/week for 3 months, with Group 2 having an additional 30 min 8 sessions over 4 weeks.		and SF-36 (all P < 0.05).	performance, QOL, and depression in the back school and exercise group than the exercise group. The benefits were persisted at 6 months follow-up."	program with exercise group.
Norbye, 2016 (score=3.5)										Wait list control bias. Data suggest similar efficacy at 12 month follow-up between groups for return to work (RTW) between groups with a slight trend toward WL group returning earlier.
Pain Management										
Kool, 2005 (score=8.0)	Back School	RCT	Supported by Swiss Federal Office of Health (Grant no. 00.00437). No mention of COIs.	N = 174 age 20-55 and non-acute non-specific LBP	Mean age of FCT group: 41.6, PCT group: 42.5; 137	Pain centered (PC) treatment to reduce pain 2.5 hours a day, 6 days a week for 3 weeks	Follow-ups to 3 months.	Days at work after 3 months post-treat: FC 25.9±32.2 vs. PC 15.8±27.5, p = 0.029. Lifting capacity change after treatment:	"Function-centered rehabilitation increases the number of work days, self efficacy, and lifting capacity	Data suggest pain-centered treatment inferior to function-centered over 3 months. No

					males, 37 females.	(n = 87) vs. Function centered (FC) treatment to increase work related capacity 4 hours/day, 6 days a week for 3 weeks (n = 87).		floor-waist 2.3±5.4 vs. 0.2±3.9, p = 0.004. Perceived effect after treat: physical capacity 4.1±2.1 vs. 2.9±1.7, p <0.001; general well-being 4.0±2.1 vs. 3.1±1.9, p = 0.005; overall improvement 4.4±2.0 vs. 3.6±2.0, p = 0.009. Pain change: post treat: 0.25±2.1 vs. 0.55±1.9, p = 0.23; 3 months NS.	in patients with nonacute nonspecific LBP."	long-term follow-ups. Study in Switzerland and not clear how applicable elsewhere.
Buhrman, 2011 (score=6.0)	Back School	RCT	Grant from Swedish Council for Working and Life Research. No mention of COIs.	N = 54 with chronic back pain ≥3 months, on sick leave from work, who have internet access.	Mean age: 43.2 Sex(M:F) 17:37	Self-help on-line management program (iCBT) (n = 26) vs. Control (n = 28).	12 weeks	Groups not different in any variables except catastrophizing (p=0.003). Quality of life decreased in controls (1.8 (SD 1.5) to 1.1 (SD 1.6)) vs. intervention (1.2 (SD 1.4) to 1.7 (1.4).	"[T]his study suggests that iCBT can result in a decrease in catastrophizing and an improvement in quality of life…"	Data suggest reduced catastrophizing although most results not significant.
Chiauzzi, 2010 (score=4.0)	Back School	RCT	Small Business Innovation Research (SBIR) Phase II grant (#9R44DA022802-02) from National Institute on Drug Abuse. No mention of COIs.	N = 209 with back pain lasting 10 days each month for 3 months with spinal origin of pain.	Mean age: 46.14. Sex(M:F) 64:134	ACTION-Back Pain educational web site (n = 104) vs Back pain information only (n = 105).	3, 6 months	At posttest the treatment group reported greater improvements of global pain intensity compared to control (p <0.05).	"[P]ainACTION-Back Pain, an online self-management program for persons with chronic back pain, is helpful in reducing pain and stress, and improving coping abilities."	Data suggest intervention may be more efficacious for multiple outcomes.
Other										

Frost, 1995 (score=7.5)	Back School	RCT	No mention of COIs.	N = 81 moderately disabled chronic LBP subjects for at least 6 months	Mean age of fitness group: 34.2, Control group: 38.5. Sex(M:F) 34:37	Fitness program plus back school (n = 36) vs. Back school (n = 35). Fitness program 8 1-hour sessions for 4 weeks (warm up and stretching, then circuit of 15 progressive exercises, then stretching and "light aerobic" exercise, psychological principles taught by physiotherapist, and avoidance of discussion of pain). All given exercises to perform at home.	6 months	Sensory pain score mean±SD before/after for fitness group vs. education group: 20.9±12.3/12.1±9.9 vs. 25.6±17.9/22.1±20.1, p <0.05. Disability Oswestry scores: 23.6±9.7/17.6±10.9 vs. 23.6±12.3/21.7±13.6, p <0.005. Walking distance (m): 445±140.8/553.7±154.5 vs. 408.9±166.4/421.4±167.4, p <0.005.	"[M]oderately disabled patients with chronic low back pain who attend a back school and fitness programme benefit more in the short and long term than patients who attend a back school and exercise independently at home."	Data suggest fitness exercise of additive benefit to back school, including at 6 months.
Cherkin, 2001 (score=7.0)	Back School	RCT	Grant from Group Health Cooperative, The Group Health Foundation, and John E. Fetzer and Grant (HS09351) from Agency for Healthcare Research and Quality. No mention of COIs.	N = 262 with subacute and chronic LBP	Mean age: 44.9 Sex(M:F) 110:152	Traditional Chinese acupuncture (n = 94) vs. Massage (n = 78) vs. Self-care education (n = 90) for 10 weeks	4, 10, and 52 weeks.	At 10 weeks, massage superior to self-care for symptom scale, (3.41 vs 4.71; p = .01) and disability scale (5.89 vs 8.25; p = 0.01). Massage also superior to acupuncture on disability scale (3.08 vs 4.74; p = .002) After 1 year, massage no longer	"Traditional Chinese Medical acupuncture was relatively ineffective. Massage might be an effective alternative to conventional medical care for persistent back pain."	Lack of control group limits conclusions. Study results suggest all groups improved, with additional benefit in therapeutic massage group compared with acupuncture. However,

								better than self-care but still superior to acupuncture on symptom scale (3.08 vs. 4.74, p = 0.002), dysfunction scale (6.29 vs 8.21, p = .05).		outcome is of uncertain clinical significance. Massage not well described.
Lamb, 2010 (score=6.0)	Back School	RCT	Funding National Institute for Health Research Health Technology Assessment Programme. No mention of COIs.	N = 705 with at least moderate LBP for >6 wks.	Mean age of Control group: 54, Intervention group: 53. Sex(M:F) 285:420	Active management + Cognitive behavioural intervention or AM + CBA for 2-day training on goal setting + pacing + challenging beliefs + managing pain + improving communication (n = 468) vs. Advice management alone for 15 minutes nurse consultation + back book (n = 233).	Follow-up at 3, 6, 12 months.	Advice plus cognitive behavioral group improved significantly compared to the control group in every measurement except short-form health (SF-12) survey (p <0.001) at 12 months.	"[C]ognitive behavioral intervention package for low-back pain has an important and sustained effect at 1 year on disability from low-back pain at a low cost to the health-care provider."	Large sample size. Subacute and chronic low back pain. Data suggest less disability with CBI group over 1 year.
McKenzie Approach										
Cherkin 1998 (7.0)	Back School	RCT	Grant (HS07915) from Agency for Health Care Policy and Research. No mention of COIs.	N = 323 who saw primary care physician and still had LBP 7 days after	Mean age: 40.7±10.7 Sex(M:F) 167:154	McKenzie approach PT (9 sessions, n = 133) vs. Chiropractic	2 years	Booklet (n = 65) vs. chiropractic (n = 119) vs. PT (n = 129) bothersome of symptoms mean (95% CI), and	"[T]he McKenzie method of physical therapy and chiropractic manipulation had similar effects and	Considerable prescription of exercise in chiropractic group, thus assessment of

						manipulation (short-lever, high-velocity thrust/9 sessions, n = 122) vs. educational booklet (n = 66) for 4 weeks.		Roland Disability mean (95% CI) measured at baseline: 5.3 (4.9-5.7)/5.5 (5.1-5.8)/6.0 (5.6-6.5)/p unadjusted = 0.04, 11.7 (10.4-13.0)/12.1 (11.2-13.1)/12.2 (11.2-13.1)/p unadjusted = 0.83. Booklet (n = 63) vs. chiropractic (n = 118) vs. physical therapy (n = 117) at 12 weeks: 3.2 (2.4-4.0)/2.0 (1.6-2.4)/2.7 (2.2-3.2)/p unadjusted = 0.02/p adjusted = 0.06, 4.3 (3.1-5.5)/3.1 (2.4-3.9)/4.1 (3.2-5.0)/p unadjusted = 0.15/ p adjusted = 0.28.	costs, and patients receiving these treatments had only marginally better outcomes than those receiving the minimal intervention of an educational booklet."	value of manipulation not possible. Data suggest PT and manipulation/ exercise superior to educational booklet, although magnitudes of benefits modest. Baseline differences with less pain in chiropractic group. No differences in outcomes other than costs reported between booklet, and McKenzie exercise protocol.
Filiz, 2005 (score=6.5)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI).	N = 60 attending an outpatient clinic after having single-level discectomy	Mean age: 39.9; Sex: 31 males, 29 females.	Intensive exercise plus back school education (4 sessions a week plus 1.5 hour intensive exercise 3 times a week for 8 weeks, N = 20) vs. home exercise plus back school	8 weeks	Intensive exercise+ back school vs. home exercise + back school vs. control post-treatment mean±SD for RTW (days), lumbar Schober (cm), VAS, back endurance, abdominal endurance, modified ODI, back depression inventory, LBP	"[P]ostoperatively applied education and exercise applications should be part of treatment with respect to the patients' earlier return to work and quicker recovery."	Data suggest intensive exercises superior.

						education (4 sessions a week plus McKenzie exercises 3 times a week, n = 20) vs. Control (n = 20). Subjects received interventions 30 days post-discectomy.		rating scale: 56.07± 18.66/75± 29.94/86.25±27.11/ p <0.001, 14.05±0.81/13.55±0 .86/12.75±0.79/p <0.001, 4.50±1.59/12±3.67/ 13.25±7.34/p <0.001, 294±90.45/188±73. 88/96±40.93/ p <0.001, 236±88.46/161.75± 69.44/65.25 ±37.99/p <0.001, 7.05±4.87/11.65±7. 21/ 15.10±8.55/p <0.001, 4.15±4/6.3±6.99/ 6.5±7.03/p <0.001, 7.40±6.92/22.45± 13.94/39.6±20.54/p <0.001.		
Stankovic, 1990 (score=4.5)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI).	N = 100 with acute LBP	Mean age: 34.4 ± 9.7; Sex: 77 males, 23 females.	McKenzie exercises for 20 for 2 weeks minutes (n = 50) vs. Mini-back school lesson once for 45 minutes (n = 50).	3 & 52 weeks.	McKenzie group RTW earlier (100% at 6 weeks vs. 11 weeks, p <0.001). Mean sick leave duration shorter with McKenzie (11.9±6.5 days vs. 21.6±15.3, p <0.001). More LBP recurrences in 1st year of observation for mini-back school (27 vs. 9, p <0.001). McKenzie group fewer episodes recurrent LBP (30 vs. 37, p <0.01) and sick leave (24 out of	"Treatment according to the McKenzie principle is in this study superior to 'mini back school'."	Study suggests benefit of stretching/exercise per McKenzie protocol for acute LBP provides greater benefit than education alone. No details on co-intervention control and low compliance to protocol limits conclusions.

								47, 51.1% vs. 31 out of 42, 73.8%, p <0.03).		
Stankovic 1995 (score=4.5)	Back School	RCT	See above.	See above.	See above.	See above.	5 years	After 4 years, McKenzie Group less LBP recurrences than mini back school group (p <0.01). McKenzie group less sick leave (p <0.03). No differences between groups for help with treatment, ability to self help, number of attacks during recurrences, positions/activities that caused pain to recur, or physical activities and smoking.	"Two conclusions can be drawn from the study: 1) the difference between groups was much less after 5 years compared with 1 year, and 2) patients who received treatment according to McKenzie principle 5 years earlier had significantly less recurrences of pain and had significantly less sick leave."	Five-year follow-up.
Back School Education										
Frost, 1998 (score=6.5)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI)	N = 81 moderately disabled chronic LBP subjects for at least 6 months	Mean age of Fitness group: 35.4 ± 9.1, Control group: 40.2± 9.2. Sex(M:F) 28:34	Fitness program plus back school (n = 31) vs. Back school (n = 31). Fitness program 8 1-hour sessions for 4 weeks (warm up and stretching, then circuit of 15 progressive exercises, then stretching and "light aerobic" exercise,	2 years	Fitness plus back school vs. back school mean±SD (range) Oswestry questionnaire score (%) at pre-treatment, 6 months, and 2 years: 23.1±9.5 (2-46)/24.9±12.8 (4-48), 16.0±9.2 (0-38)/21.7±14.2 (0-50), 15.4±11.3 (0-52)/22.5±15.4 (2-64). Fitness plus back school with reduction (p <0.001)	"Exercise can take many forms and we have demonstrated benefits of a general non-specific fitness programme designed for patients with chronic low back pain."	Data suggest fitness of additive benefit to back school and benefits persisted at 2 years. Used CBT.

						psychological principles taught by physiotherapist, and avoidance of discussion of pain). All given exercises to perform at home.		of 7.7% vs. 2.4% in back school (p >0.05). Difference in ODI mean (95% CI): 5.8 (0.3-11.4), p <0.04.		
Hazard, 2000 (score=6.5)	Back School	RCT	Grant H133E30014–95 from National Institute on Disability and Rehabilitation Research. No mention of COIs	N = 486 who filed an occupational back-related injury	Mean age: 37.6; Sex: 274 males, 176 females.	*Good News About Back Pain* pamphlet (sent 11 days after injury, n = 244) vs. No pamphlet (n = 245).	Final follow-up at 6 months.	Pamphlet vs. no pamphlet primary outcome for disability (% not working), and mean±SD lost work days measured at 3 months: 7.9%/7.7% (p = 1.00), 18.7±42.5/18.2±41.5 (p = 0.90). At 6 months: 6.5%/5.9% (p = 0.84), 19.1±43.2/18.1±42.8 (p = 0.83). Changed/modified jobs differed at 3 months, p = 0.002.	"The results of the present study do not suggest any advantage of psychosocially oriented recovery advice compared with the equivocal impact of more traditional biologic approaches common in back schools."	Data suggest education booklet ineffective.
Burton, 1999 (score=6.0)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI).	N = 162 with acute non-specific LBP <3 months	Mean age: 43.6; Sex: 73 males, 89 females.	Back book (evidence-based information and advice consistent with current clinical guidelines, N = 83) vs. Handy hints control (N = 79).	Final follow-up at 1 year.	Back book vs. handy hints mean±SD baseline pain at worst, baseline pain at best, pain at worst 1 year, and pain at best 1 year: 71.5±19.2/68.7±18.5, 15.8±17.5/15.6±18.7, 50.9±29.6/50.8±27.8,	"This trial shows that carefully selected and presented information and advice about back pain can have a positive effect on patients' beliefs and clinical outcomes, and suggests that a study of clinically	Data suggest addressing FABs is effective.

								10.1±16.6/10.6±17.8. Mean belief scores differed at 2 weeks (p = 0.02), 3 months (p = 0.02), and 1 year (p = 0.05).	important effects in individual patients may provide further insights into the management of low back pain."	
Heymans, 2006 (score=6.0)	Back School	RCT	Granted by The Netherlands Organization for Health Research and Development (Zon/Mw), Dutch Ministries of Health, Welfare and Sports and of Social Affairs and Employment. No mention of COIs.	N = 300 workers sick listed for 3 weeks because of non-specific LBP	Mean age: 40.27; Sex: 236 males, 63 females	High-intensity back school (1 hour sessions, 2 times a week for 8 weeks and including CBT, n = 98) vs. Low-intensity back school (weekly group sessions for 4 weeks, n = 98) vs. Care as usual (n = 103).	Final follow-up at 6 months.	Low intensity vs. usual care/high intensity vs. usual care/low intensity vs. high intensity hazard ratios (95%CI) ITT, per protocol analysis, and complete case analysis: 1.4 (1-1.9)/1 (0.8-1.4)/1.3 (1-1.8), 1.4 (1-1.9)/0.9 (0.6-1.2)/1.6 (1.1-2.3), 1.4 (1-2)/1.1 (0.8-1.5)/1.3 (1-1.9). P value: p = 0.06/p = 0.83/p = 0.09, p = 0.06/p = 0.39/p = 0.01, p = 0.03/p = 0.68/p = 0.09. Differences in kinesiophobia and functional status for low intensity vs. usual care at 3 months: p = 0.00, p = 0.01.	"[L]ow-intensity back school has beneficial short-term effects compared with care as usual and a high-intensity back school on sick-leave, functional status, and kinesiophobia."	Study based in the Netherlands and unclear if prolonged durations of time off work and population studied apply elsewhere.
Triano, 1995 (score=5.5)	Back School	RCT	Grants from Lincoln College Education and Research, and foundation for Advancement of Chiropractic	N = 209 with chronic LBP >50 days duration or at least 6 episodes in prior year	Mean age: 41.6 Sex(M:F) 113:96	Chiropractic adjustments, n = (high-velocity, low-amplitude spinal manipulation) vs. sham	2 weeks after treatment.	Oswestry scores chiropractic manipulation 17.5±12.8 to 9.5±6.3 at 2 weeks to 10.6±11.7 at 4 weeks vs. sham 21.7±15.0 to	"In human terms, however, there appears to be clinical value to treatment according to a defined plan using manipulation even	Attempted sham and blindings strengths, but study not truly blinded other than assessor and potentially blinded patient

			Education. No mention of COIs.			adjustments (high-velocity, low-force mimic) vs. back education program (no exercises) for 2 weeks of treatment 6 days a week		15.5±10.8 to 14.0±11.7 vs. education: 20.2±13.6 to 12.3±8.4 to 11.4±10.3, p = 0.012 between groups at 2 weeks. VAS scores: DC 38.4±23.4 to 13.9±15.3 at 2 weeks to 13.3±15.9 at 4 weeks vs. sham 37.4±23.7 to 19.8±18.3 to 21.7±24.4 vs. education: 35.6±23.0 to 19.6±17.6 to 15.1±19.4. Zung scores were not significant between groups.	in low back pain exceeding 7 weeks duration."	(belief in sham vs. true not reported). Many baseline data not given; dropouts high. No intermediate or long-term follow-up. ODI only favored manipulation at intermediate. At 4 weeks, no difference between chiropractic manipulation and back education. Data do not support conclusion of manipulation efficacy compared to education treatment.
Indahl, 1998 (score=5.5)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI).	N = 489 with sub chronic LBP lasting 4-12 weeks in Norway	Mean age: 41.6; Sex: 306 males, 183 females.	Standard medical care (control, n = 244) vs. Mini back school (intervention, n = 245).	Final follow-up at 5 years.	After 5 years, 81% of intervention group vs. 65% of controls had returned to work. Rates of permanent disability higher in controls (19% vs. 34%).	"Informing patients with subchronic LBP about the nature of their problem, in a manner designed to reduce fear and give them reason to resume light normal activity as a form of treatment, may reduce long-term disability."	Unclear if study population with such prolonged time away from work applies to U.S. or elsewhere. Those not returning to work were less physically active.
Leclaire, 1996 (score=5.0)	Back School	RCT	Grant RS-87-35 from Institiut de recherché en	N = 168 workers with acute LBP <3	Mean age of back school	Daily physiotherapy +	Final follow-up	Improvement in functional disability favored daily	"A back school intervention in addition to	Rates of recurrences worse in back

			sante et en securite du travail du Quebec. No mention of COIs.	months (mean = 15 days)	group: 31.9, Standard therapy group: 32.2. Sex(M:F) 98:70	back school (n = 82) vs. Daily physiotherapy (N = 86). Daily physiotherapy program consisted of rest, NSAIDS, daily, and analgesics. Back school three 90-minute session at 0, 1, and 8 weeks.	at 12 months.	physiotherapy vs. back school with ODI and Roland-Morris scores, p = 0.02, p = 0.01. At end of treatment, improvements in mobility/SLR Schober test favored daily physiotherapy vs. back school: p = 0.01. Back school showed gain in knowledge and performed exercise program better: p = 0.0001, p = 0.0001.	standard care resulted in no reduction in the time to return to work or the number or duration of recurrences of low back pain requiring compensation over a period of 1 year."	school group, and back school intervention in addition to standard care resulted in no reduction in RTW time or number or duration of compensable LBP recurrences over 1 year.
Cairns, 2006 (score=5.0)	Back School	RCT	No funds received in support of this work. No benefits in any form have been or will be received from commercial party related directly or indirectly to subject of this manuscript. No mention of COIs.	N = 97 with chronic LBP mean 9.6 and 7.9 months duration	Mean age of Stabilizatio n group: 37.5, Convention al group: 39.9. Sex(M:F) 47:50	Stabilization with physiotherapy (n = 47) vs. Usual physiotherapy (n = 50). Initial assessment 60 minutes with 30 minutes follow-up totaling 12 treatments over 12 weeks. Spinal stabilization exercise group focused on endurance training for deep abdominal and back extensor muscles.	6 & 12 months	Most received exercises other than stabilization exercises (100% of conventional group and 45/47 = 94% of stabilization), plus many other treatments and modest differences in manual therapy between 2 groups – manual therapy 38 (76%) vs. 32 (67%). No differences between groups for Roland and Morris disability, ODI, modified Zung, modified somatic perception questionnaire, distress risk assessment method, short form McGill	"Patients with LBP had improvement with both treatment packages to a similar degree. There was no additional benefit of adding specific spinal stabilization exercises to a conventional physiotherapy package for patients with recurrent LBP."	Dropout rate 30% in each group. Many co-interventions. No control or sham group. Data suggest stabilization specific exercise not beneficial in addition to conventional PT treatment; however, study weaknesses preclude strong conclusions.

								pain questionnaire, or quality of life.		
Moseley, 2004 (score=5.0)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI).	N = 58 with CLBP >6 months.	Mean age of Experimental group: 42±10, Control group: 45±6. Sex(M:F) 25:33	Education sessions on neurophysiology of pain (3 hour sessions 5 days a week for 2 weeks, n = 31) vs. Back education (n = 27) for duration of 2 weeks.	15 weekdays	Neurophysiology vs. back school had higher SOPAR + PCS scores at post-treatment, p <0.0001. Neurophysiology group vs. back school with difference in seeking care when in pain, controlling pain, and perceiving as less disabled: p = 0.024, p = 0.002, p = 0.022. Pre-/post-treatment raw scores for self-reported and physical performance effect size(95% CI) for RMDQ, SOPA (seeking care from others), SOPA(emotions affect pain), SOPA (pain controllable), SOPA total, PCS, SLR(°), and bending (cm from floor): 2 point (0.4 to 3.6), 1 point (-1.2 to -3.2), 2 (0.4 to 3.6), 2 (0.4 to 3.6), 4 (2.1 to 5.9), 9 (6.5 to 11.5), 6 (3.8 to 8.2), 5 (4 to 6), 4(0 to 8.2).	"[N]europhysiology education results in some normalization of pain cognitions and physical performance but not in self-perceived disability."	Data suggest educational program efficacy.

Sorensen, 2010 (score=5.0)	Back School	RCT	Funding granted by IMK Foundation, Health Insurance Foundation (Sygekassernes Helsefond), Tryg Foundationen, Funen County Research Foundation, and Danish RheumatismAssociation. No mention of COIs.	N = 207 age 18-60 with chronic LBP lasting at least 4 of last 12 months. Pain had to be greater in back than associated leg pain.	Mean age: 39. Sex(M:F) 99:108	Educational program (EDUC) (n = 105) vs. Physical training (TRAIN) (n = 102). Pragmatic trial.	2, 6, 12 months	Both groups improved in pain scores (p <0.001). The EDUC improved significantly in fear avoidance beliefs (p = 0.05) compared to baseline. Both groups did not significantly improve in back beliefs (p = 0.16 and 0.13).	"A cognitive intervention for cLBP resulted in at least as good outcomes as symptom-based physical training method despite fewer treatment sessions."	Different exercise Rx. Different approaches between groups. Higher dropouts in physical training, Data suggest comparable results, although fewer contacts.
Lindström, 1992 (score=4.5) .	Back School	RCT	Supported by Arhetsmarknadens forsakringsaktiebolag (MA), Stockholm, Sweden; Volvo Company, Goteborg, Sweden; Medical Faculty of University of Goteborg, Goteborg, Sweden; AMF-Trygghetsforsakring, Stockholm, Sweden; Greta and Einar Asker Foundation Goteborg, Swedcn; and Knha and Felix Neuberg Foundarion, Goteborg, Sweden. No mention of COIs	N = 103 with subacute LBP off work for 6 weeks	Mean age of activity group: 39.4, Control group: 42.4. Sex(M:F) 71:32	Graded activity group (n = 51) vs. Controls: no treatment (n = 52) for 1 year. Graded activity group with measured functional capacity (mobility, strength and fitness), workplace visit, back school education, and an individual, submaximal gradually increased exercise program with operant conditioning.	2 years	Increases in arm strength, abdominal muscle strength, back muscles, and many other outcome measures preserved at 1 year in activity group. Activity group RTW 5.1 weeks earlier, p = 0.03.	"The patients with subacute, nonspecific, mechanical LBP who participated in the graded activity program regained occupational function faster than did the patients in the control group, who were given traditional care."	Involved orthopedic surgery and physiotherapy. GPs administered routine care, but not otherwise involved in trial. Social worker performed psychosocial screening. Graded activity program reduced long-term sick leave, especially in males. Intensive exercises, work-hardening exercises, or expensive equipment not necessary to regain occupational function.

Daltroy, 1997 (score=4.5)	Back School	RCT	Grant (AR36308) from National Institutes of Health. No mention of COIs.	N = 3,597 U.S. postal workers with LBP	Mean age of Intervention group: 43.0 ± 12 0, Control group: 42.0±12.5. Sex(M:F) 2681:916	Employee-back education programs (n = 1703) vs. Control (n = 1894).	Final follow-up at 5.5 years.	Differences in seasonal lifting-and-handling injuries between groups, p <0.001. Differences in total costs, medical costs, and personnel-replacements costs for workers with LBP history vs. workers with no LBP history: p = 0.005, p = 0.03, p = 0.004.	"A large-scale, randomized, controlled trial of an educational program to prevent work associated low back injury found no long-term benefits associated with training."	No reductions in injuries, lost time, or recurrences of injuries. Data suggest no long-term benefits associated with training.
Sahin, 2011 (score=4.5)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI).	N = 146 with chronic LBP longer than 12 weeks without neurological deficits.	Mean age of BSG group: 47.25, CG group: 51.36. Sex(M:F) 34:112	Back school plus physiotherapy (BSG) (n = 75) vs. Physiotherapy alone (CG) (n = 75) for 2 weeks.	3 months	BSG improved significantly compared to CG in VAS pain and Oswestry (ODQ) scores (p=0.010 and p <0.001) at post-treatment and 3 months (p = 0.002 and p <0.001).	"[A] back school programme has an effect on pain and disability when given in addition to physical treatment modalities and exercises."	Limited generalizability due to exclusion criteria.
Walsh, 1990 (score=4.0)	Back School	RCT	Grant 88-0331 Institutional Biomedical Research. No mention of COIs.	N = 90 grocery warehouse workers (to prevent LBP)	Mean age: 29.4; No mention of Sex.	Back school one 1-hour session (Group 2, n = 27) vs. Back school and lumbosacral orthosis (Group 3, n = 27) vs. control group (Group 1, n = 27) for 6 months.	6 months	Abdominal muscle strength increased in all groups and increased most in back school plus orthosis group. Lost days in controls changed from 0.4±0.2 to 0.8±0.5 (6 months previously vs. 6 months during the study). In back school group, lost days changed from 3.2±1.9 to 2.6±1.6 vs. 2.9±1.2 to 0.5±0.4 for combination group.	"It appears that the use of intermittent prophylactic bracing has no adverse effects on abdominal muscle strength and may contribute to decreased lost time."	Abdominal muscle strength measured, but not back muscle strength. Authors concluded results support combination of education and bracing but no bracing-only group, and education appeared to have no effect. Lost days in 6 months pre-study markedly different in

										groups at baseline, suggests randomization failure.
Hurri, 1989 (score=4.0)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI).	N = 188 workers with chronic LBP ≥12 months in Sweden	Mean age: 46.1±9.5 for treatment group, 45.4±9.2 for control group; 0 males, 188 females.	Swedish back school (n = 95) vs. handout containing information presented at back school (n = 93). Swedish back school consisted of 60 minute education plus exercise 6 times within 3 weeks. Final follow-up at 12 months.	12 months	Differences for Swedish back school group for mean VAS at 6, 12 months: p = 0.01, p = 0.05. Swedish back school vs. control mean pain index differences at 6, and 12 months: p = 0.01/NS, p = 0.01/p = 0.05. Differences in Swedish back school for forward flexion 1(cm), right lateral flexion (cm), left lateral flexion (cm), stomach muscle exercises (max 10), static trunk extension strength (kp), flexion strength (kp), pain during forward flexion, pain during lateral flexion of spine, and pain during dynamic back muscle exercise at 12 months: p = 0.001, p = 0.001, p = 0.01, p = 0.05, p = 0.001, p = 0.001, p = 0.05, p = 0.05, p = 0.01. Differences in control for forward flexion2 (cm), right lateral flexion (cm), and left lateral flexion (cm) at	"[C]hronic low back pain patients may benefit from the back school regimen."	VAS pain scores favored back school. No change in sick leave with back school. Impacts may be contextual (Finland).

								12 months: p = 0.01, p = 0.05, p = 0.05.		
Tao, 2005 (score=4.0)	Back School	RCT	Supported by Procter & Gamble Company. No mention of COIs.	N = 43 with work-related acute muscular LBP	Mean age of Treatment group: 35.0, Reference group: 36.2. Sex(M:F) 7:36	Education only: written materials describing LBP (n = 18) vs. Education with ThermaCare Heat Wrap: heat wrap worn 3 consecutive days during daytime hours and taken off at end of each day (n = 25).	Follow-up Days 4, 7, and 14.	Pain intensity (Day 0/Day 14): heat wrap (0.00/-3.85) vs. education (0.0/-2.22), p = 0.0046). Pain relief (Day 0/14): heat wrap (0.00/4.04) vs. education (0.00/2.83), p = 0.0032. Roland Morris Score (Day 0/14): heat wrap (0.00/-6.55) vs. education (0.00/-2.53), p = 0.0026.	"[H]eat wrap therapy using ThermaCare Heat Wrap significantly reduced pain intensity, increased pain relief, and improved disability scores during and after treatment adjusting for sex, age, baseline pain intensity, and pain medications."	Education as comparison may have biased in favor of Heat Wrap.
Larsen, 2002 (score=4.0)	Back School	RCT	Industry sponsored by foundation funds. No COI.	N = 314 male present at regiment infirmary at prescribed medical check during first week of military service and willingness to participate.	Mean age: 21±1.5; Sex(M:F) 314:0	Intervention group at baseline, all conscripts participated in back school lesson lasting 40 minutes (n = 150) vs. Control group at baseline, there was no intervention in the control group, and no attempt was made to ensure that conscripts did not perform the same	Follow-up for 10 months.	The baseline characteristics for the study population did not significantly differ on any characteristics from total baseline population. Intent-to-treat analysis; at follow-up there were no significant differences between the two groups the last 3 weeks. No significant differences between groups at follow-up in the group seeking medical care because of back	"It may be possible to reduce the prevalence rate of back problems and the use of health care services during military service, at a low cost, using passive prone extensions of the back motivated by a back school approach, including the theory of the disc as a pain generator and ergonomic instructions."	Many weaknesses. High dropouts. Data suggest exercise may prevent LBP.

						exercises (n = 164).		problems preceding military service: 4 or 25% in the intervention group versus 6 or 25% in the control group, p = 1.000. Worst-case analysis; there was 1 year lower prevalence of back problems in the intervention compared to control group, 45 % compared to 57%, p = 0.025.		
Maastricht Back School										
Keijsers, 1989 (score=4.0)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI).	N = 30 with LBP >6 months in the Netherlands	Mean age: 49.7 years; 12 males, 18 females.	Maastricht Back School (7 1.5 hour sessions, n = 16) vs. WLC (n = 14).	Final follow-up at 8 weeks.	Pre-post test score differences between groups for somatic fixation, internal locus of control, and seeking social support: p <0.05, p <0.01, p <0.01.	"The results suggest that the Back School program for patients with chronic low back pain can have a positive effect."	Small groups. Most variables not significant. Smaller sample than Keijsers 1990 article to address same topic.
Keijsers, 1990 (score=4.0)	Back School	RCT	No mention of industry sponsorship or conflict of interest (COI).	N = 77 with LBP ≥2 months in the Netherlands	Mean age: 35.8; 39 males,38 females.	Maastricht Back School Vs No treatment.	Final follow-up at 6 months.	At 6 months, differences in time and condition between groups: p = 0.001, p = 0.001.	"Although bias cannot be excluded from our study results, it does not seem likely that the Maastricht Back School is an effective method of managing LBP."	Data suggest lack of efficacy.
Bio Education – LBP										
Ryan, 2010 (score=4.5)	Back School	RCT	Funded by School of Health and Social Care of	N = 38 age 18-65 with non-specific	Mean age: 45.3;	Pain biology education (ED) (n = 18) vs. Pain	3 months	Pain rating (0-100) and pain efficacy (0-60) improved	"[P]ain biology education was more effective for	High dropout rate. Baseline differences.

			Glasgow Caledonian University. No mention of COIs.	LBP lasting longer than 3 months and no history of back surgery.	Sex: 13 males, 25 females	biology education with physical exercise (EDEX) (n = 20).		significantly in the ED group compared to EDEX (p=.025 and p=0.024). Groups were not significantly different in function, pain related fear, 5 minute walk, or free-living step count.	pain and pain self-efficacy than a combination of pain biology education and group exercise classes…"	
Chok, 1999 (score=4.5)	Back School	RCT	No mention of industry sponsorship or COI.	N = 66 with acute and subacute LBP.	Mean age: 36.03; Sex: 41 males, 13 females.	Endurance training of the trunk extensor muscles (n = 30) vs, Control (n = 24).	6 weeks	Improvements at 3 weeks for VAS (p <0.05), and disability score (p <0.05). No differences at 6 weeks.	"Endurance exercise is considered to expedite the recovery process for patients with an acute episode of low back pain."	Significant baseline differences present. Many weaknesses in methods preclude strong conclusions.
Meng, 2011 (score=4.0)	Back School	RCT	Funded by Deutsche Rentenversicherung Bund (German Statutory Pension Insurance Scheme), Berlin, Germany. No mention of COIs.	N = 382 with LBP	Mean age: 49.8; Sex: 129 males, 231 females.	Biopsychosocial back school program (manual based and interdisciplinary) (n = 197) vs. Traditional back school program (usual care) (n = 185).	6 & 12 months	Biopsychosocial back school group improved significantly in knowledge of back exercises (p = 0.021), cognitive restructuring (p = 0.007), counter-activities (p = 0.007), and relaxation (p = 0.007) compared to the traditional school.	"…Results showed a significant medium treatment effect in patients' knowledge about chronic back pain and its treatment at discharge of rehabilitation as well as 6 and 12 months after the program."	High dropout rate in both groups. Results suggest that intervention more efficacious at 6 months compared to traditional back school program
Other										
Loisel, 2002 (score=4.0)	Back School	RCT	Grant sponsor: Institut de Recherche en Santé et Sécurité au Travail du	N = 104 workers with LBP absent from work ≥4	Mean age: 40.7; Sex: 62 males, 42 females.	Standard care (n = 26) vs. occupational intervention (n = 22) vs. clinical	Mean follow up 6.5 years.	Differences between groups for number of subjects exceeding total cost	"A fully integrated disability prevention model for occupational back pain	Large number of days on full benefit (DFB) saved in partial interventions

			Québec (IRSST). No mention of COIs.	weeks in Canada		intervention (n = 31) vs. occupational+ clinical arm (n = 25). Clinical arm and occupational plus clinical arm: back school 8 weeks after work absence. Reassurance through OM physician, back pain specialist, and/or health care professionals in rehab interventions. Early return to normal activity encouraged, early workplace support promoted by ergonomic intervention and/or therapeutic RTW program.		of $65,000, p = 0.0201.	appeared to be cost beneficial for the workers' compensation board and to save more days on benefits than usual care or partial interventions."	arms and larger numbers of DFB saved in Sherbrooke model, with lesser consequence of disease costs. Effective mix of interventions to reduce total costs is unclear.
van Poppel, 1998 (score=4.0)	Back School	RCT	Grant 28.2672.6 from the Praeventiefonds, the Hague, the Netherlands. No mention of COIs.	N = 312 airline cargo workers in the Netherlands	Mean age: 35.1; No mention of Sex.	Lifting instructions (3 sessions for groups of 10-15; 1st session 2 hours at start of intervention,	Follow-up for 6 months.	Despite choice of support in pilot testing, compliance with wearing supports at least half time low (43%). No differences in	"[L]umbar supports or education did not lead to a reduction in low back pain incidence or sick leave.	Considering objects likely large sized, lift with knees not back requirement almost

						other sessions 1.5 hours given at 6 weeks and 12 weeks) and lumbar support (n = 70) Vs Lifting instruction (n = 82) vs Lumbar support (n = 83) vs No intervention (n = 77).		LBP incidence or lost-time injuries. In workers who never had LBP, incidence higher among those using support. IF LBP at baseline, lost-time injuries were reduced with support (median 1.2 days/month vs. 6.5 days/month). Among workers compliant with supports, LBP reporting not statistically increased.		completely infeasible due to human strength considerations (potentially substantiated by statement that 11% stated they lifted as taught all the time, 73% some of the time, 11% never).

Evidence for Chronic Pain Management Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Nicholas, 2014 (score=7.0)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Sponsored by the Australian Health Ministers Advisory Council. No COI.	N = 141 patients with chronic pain.	Mean age: 73.90 years; 52 males, 89 females.	Pain Self-Management Group (PSM) (n= 49) – Patients received intervention based on cognitive behavioral pain management skills. Vs. Exercise-Attention Control Group (EAC)	1 month.	For RMDQ, the adjusted mean (95% CI) value of PSM vs EAC is 2.68 (p=0.004), PSM vs WL is -2.65 (p=0.001), EAC vs WL is 0.03 (p=0.90).	"In the short term at least, cognitive-behavioral therapy based PSM was more effective than exercises and usual care."	Waitlist control bias. Data suggest cognitive behavioral therapy self-management is better than usual care or exercise alone for chronic pain in older adults at 1 month.

						(n= 53) – Participants were able to choose at home exercise performance. Vs. Waiting List Control Group (n=39) - performed measures at baseline and at 12 weeks, without any intervention.				
Dear, 2015 (score=6.5)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Sponsored by the Motor Accidents Authority of New South Wales and the National Health and Medical Research Council (NHMRC) to B. F. Dear through an Australian Public Health Fellowship. No COI.	N=490 patients with chronic pain conditions.	Mean age: 50 years; 96 males, 375 females.	Regular Contact (n=143) – Participants participating in the Pain Course were assigned to a clinician who provided weekly contact to patients for 10-15 mins per contact. Vs. Optional Contact (n=141) – Patient participating in the Pain Course were given the option to contact the clinician.	Baseline, 8 weeks, 3 month follow up.	The between-group Cohen's d effect sizes at posttreatment RMDQ score for regular contact and the following groups: -0.02 optional contact, 0.06 no contact, 0.53 waitlist control; for optional contact and the following groups: 0.07 no contact, 0.54 waitlist contact; for no contact and the following groups: 0.50 waitlist control. PHQ-9 d effect sizes at posttreatment were 0.18 regular	"…[T]he present study replicates and extends the findings of an earlier trial. Significant improvements in levels of disability, anxiety, depression, and pain were observed and no consistent or marked differences were found across the levels of clinician support provided."	Waitlist control bias data suggest an internet-delivered pain management program can improve anxiety depression pain and disability in lieu of varying levels of clinical support.

						Vs. No Contact (n=131) – Patients were informed they would not revive contact during the Pain course. Vs. Control (n=75) – Treatment as usual waitlist group.		contact and optional contact, 0.15 regular contact and no contact, 0.98 regular contact and waitlist control, -0.05 optional control and no contact, 0.73 optional contact and waitlist control, 0.87 no contact and waitlist control. GAD-7 d effect sizes at posttreatment were 0.16 regular contact and optional contact, 0.06 regular contact and no contact, 0.63 regular contact and waitlist control, -0.11 optional contact and no contact, 0.44 optional contact and waitlist control, 0.61 no contact and waitlist control.		
Bair, 2015 (score=5.5)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Sponsorship by Merit Review grant from VA Rehabilitation Research and Development. Dr. Kroenken received honoraria from Eli Lilly and company outside the submitted	242 patients with chronic and disabling musculoskeletal pain.	Mean age 37.3; 213 males, 28 females.	Stepped-care intervention optimization of analgesic treatment, self-management strategies, and CBT. (N = 121) vs Usual Care (N = 120)	9 months	Change from baseline stepped-care vs Usual care RMDS s -1.9 (p = .002) BPI pain interference -.8 (p = .003) GCPS severity -6.6 (p = .001)	"Stepped-care intervention that combined analgesics, self-management strategies, and brief cognitive behavioral therapy resulted in statistically significant reductions in pain-	Usual care bias. No information on medication pre-trial. Data suggest stepped care plan significantly improved pain and disability.

			work no other COI.						related disability, pain interference, and pain severity in veterans with chronic musculoskeletal pain."	
Hutting, 2015 (score=5.0)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Sponsored by ZonMw, the Netherlands Organization for Health Research and Development. No COI.	N= 123 patients with chronic pain.	Mean age: 46.2 years; 28 males, 89 females.	Self-Management Group (SG) (n= 64) – Patients set goals and made action plans and were given information in self-management Vs. Usual Care Group (UCG) (n= 53) – Patients were able to use all usual care information within and outside the organization of the participant.	Baseline, 3 months, 6 months, 12 months.	DASH scores at baseline, 3 months, 6 months , and 12 months for SG group were 22.28, 17.76, 14.04, 14.32, p=0.10; for UCG group were 22.27, 19.55, 17.39, 15.05, respectively.	"The self-management intervention improved the participants' perceived disability during work. Since no significant between-group differences were found on most outcome measures, the results of this study should be interpreted with caution."	Usual care bias. High dropout rate in control group. Medication use missing from baseline data table. Data suggest perceived disability improvement in SG group.
Oldenmenger, 2011 (score=4.5)	Pain Education Programs	RCT	Sponsored by the Erasmus MC Health Care Research and the Erasmus MC Revolving Fund. No COI.	N = 72 patients with cancer and chronic pain.	Mean Age: 59 years; 25 males, 47 females.	Standard Care (n=37) – Patients received standard treatment. Vs. Pain Consult and PEP (n=35) –	8 weeks.	Pain treatment during the study: Patients with pain consultation: SC 13, PC-PEP 35, p<0.001; CT/MRI: SC 15, PC-PEP 26, p=0.004; Hospital Admissions: SC 8, PC-PEP 11, p=0.25;	"In conclusion, PC-PEP improves pain, daily interference, and patient adherence in oncology outpatients."	Standard care bias. Data suggest PC-PEP improves pain intensity and pain knowledge in oncology patients.

						Consisted of patient-tailored pain education and weekly monitoring of pain and side effects.		Radiotherapy: SC 10, PC-PEP 9 p=0.556.		
Kell, 2009 (score=4.5)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Sponsored by the Saskatchewan Health Research Foundation (New Investigator Grant) and the University of Alberta, Augustana Campus (travel grant).	N = 27 patients with non-specific low back pain.	The mean age of the RT group is 40.1 years. 5 males, 4 females. The mean age of the AT group is 36.7 years. 5 males, 4 females. The mean age of the Control group is 35.3 years. 5 females, 4 males.	Resistance Training (RT) (n=9) - Patients performed upper- and lower-body RT exercises that consisted of free weights and machine use. Vs. Aerobic Training (AT) (n=9) – Patients performed any aerobic exercise in which the subject was interested, with the most commonly selected modes being the elliptical trainer and treadmill walking or jogging. Vs. Control (n=9)	Baseline, week 8 and week 16.	The data of significance for muscular strength, endurance, flexibility and power is the following: Bench Press – RT group: at baseline 44.4 kg (($p \leq 0.05$) between RT and C at week 16 and ($p \leq 0.05$) within group between baseline and week 16). At week 8 54.3 kg (($p \leq 0.05$) within group between week 8 and week 16). At week 16 56.9 kg (($p \leq 0.05$) between RT and C at week 16). Sit-and-Reach flexibility (cm) at baseline: RT group 31.7 (($p \leq 0.05$) within group between baseline and week 8 and ($p \leq 0.05$) within group between baseline and week 16). AT group 24.9 (($p \leq 0.05$) within group between baseline and week 8).	"This study indicates that whole-body periodized RT can be used by training and conditioning personnel in the rehabilitation of those clients suffering with CLBP."	Relatively high dropout rate with unknown differences between groups.

Jousset, 2004 (score=4.0)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Sponsored by Union Re´gionale des Caisses d'Assurance Maladie des Pays de Loire. No COI.	N = 86 patients with low back pain.	The mean age of the Functional Restoration group is 41.4 years. 30 males, 13 females. The mean age of the active individual therapy group is 39.5 years. 26 males, 15 females.	Functional Restoration (n=43) – For 6 hours a day, 5 days a week, for 5 weeks, patients participated in the following activities: warm-up, strengthening exercises, aerobic activities, occupational therapy, endurance training, and individual interventions vs. Active Individual Therapy (n=41) – Patients received 1-hour treatment sessions, three times a week during 5 weeks. Patients were to perform exercise at home for 50 minutes.	Baseline and 6 months.	The main outcome measure is was the number of self-reported sick-leave days between the end of the program and the 6-month follow-up appointment. Number of sick-leave days for Functional Restoration group and Active Individual Therapy group is 42 and 41, respectively. (p=0.12).	"This study demonstrates the effectiveness of a functional restoration program on important outcome measures, such as sick leave, in a country that has a social system that protects people facing difficulties at work."	Data suggest the functional restoration group had a significantly lower number of sick day s than the active individualized therapy group.
Friedrich, 1998 (score=4.0)	Chronic Pain Management Programs/Functional	RCT	No mention of sponsorship. No COI.	N = 93	Mean age is 44.08; 46 males, 47 females.	Standard Exercise Program (N = 49) vs. Combined Exercise and	12 months	Pain intensity decreased in both treatment groups. Significant effects of both the time of assessment	"A program combining conventional exercise therapy with motivation-enhancing	Compliance higher in motivational groups. High 5 year dropout rate (>40%).

	Restoration Programs					Motivation Program (N = 44)		(p=.000) and treatment (p=.037) but significant time X group inter action (p = .609). Significant differences in pain ratings in favor of the motivation group (1st follow up p=.011; 4-month follow up p=.026; 12-month follow up p=.006).	intervention strategy significantly reduced the level of disability and pain in low back pain patients."	Data suggest combined motivational and exercise program better at reducing disability and pain and increases work ability in patients with chronic pain.
Roche, G 2007 (score=4.0)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Supported by the Union Regionale de Caisses d'Assurance Maladie des Pays de Loire. No COI.	N = 132	Mean age is 39.8 years; 46 females, 86 males.	FRP Group (N = 68) vs. AIT Group (N = 64)	5 weeks	No significant between the two comparison groups at baseline in regards to sex, age, depression, and lower back pain. Greater improvement for patients with lower t0 Sorensen scores. Change in score between t0 and t5 correlated with significant with the t0 score (ANCOVA, p<.001) and treatment (P<.001).	"Low-cost ambulatory AIT is effective. The main advantage of FRP is improved endurance. We speculate that this may be linked to better self-reported work ability and more frequent resumption of sports and leisure activities."	Data suggest all outcome measures improved in both the AIT and FRP groups with the exception of endurance in the AIT group. However, greater improvements were seen in ERP groups.
Roche-Leboucher, 2011 (score=4.0)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Sponsored by Institut National de veille sanitaire, Paris, France. No COI.	N=132 patients with low back pain	Mean age: 39.8 years; 86 males, 46 females.	Functional Restoration Program (n=68) – Patients performed muscle strengthening, endurance training, balneotherapy,	1 year.	The reduction in number of sick-leave days (posttreatment year – pretreatment year) for functional restoration is 64 (p<0.001) and for Active Individual Therapy is 49 (p<0.001).	"Both programs are efficient in reducing disability and sick-leave days. The FRP is significantly more effective in reducing sick-leave days. Further analysis is required to determine if	Data suggest FRP effective with less sick leave, increased fitness, and trends towards greater return to work and full time work (the latter 2 are underpowered).

						and attended psychologist meetings. Vs. Active Individual Therapy (n= 64) – Patients focused on flexibility training and pain management.			this overweighs the difference in costs of both programs."	
Dowd, 2015 (score=4.0)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	No COI. No mention of sponsorship.	N = 124 with chronic pain for more than 6 months	Mean age: 44.53 years; 12 males, 112 females.	Mindfulness in Action (MIA) (N = 62) vs. online version of pain management psychoeducation program (PE) (N = 62). Each group received 12 sessions twice a week for 6 weeks	6 months	Least Squares Mean for Pain interference at times T1 (baseline), T2 (pre-intervention), and T3 (6 month follow-up), respectfully: MIA 39.55±1.96, 24.83±2.90, 30.71±3.00. PE 44.83±2.02, 31.50±2.42, 35.47±2.69. Multilevel Model Results for Group Effects on Changes in Pain interference over time: Intercept 48.89±2.97, Group -5.20±4.22, Time -5.78±1.44 ($p<0.0001$), Time x Group 0.34±2.16.	"The results of the study provide evidence that although there were equivalent changes across outcomes of interest for participants in both conditions over time, the MIA program showed a number of unique benefits."	High dropout rate.

Guetin, 2012 (score=4.0)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Sponsored by the Foundation CNP Assurances. No COI.	N= 87 patients with lumbar pain, fibromyalgia, inflammatory disease, or neurological disease.	Mean age: 48.8 years; 19 males, 68 females.	Music Intervention (n=44) – Patients received standard therapy and individual music therapy sessions. Vs. Control (n=43) – Patients received standard treatment only.	3 months.	Pain VAS score at D0 was -1.6 and at D60 was -3.4 in the music intervention group. p<0.001. At D90 the mean score is 3.4 in the music intervention group and 4.7 in control group. P<0.001.	"These results confirm the value of music intervention to the management of chronic pain and anxiety/depression. This music intervention method appears to be useful in managing chronic pain as it enables a significant reduction in the consumption of medication."	Data suggest short term benefit of music therapy for decreasing anxiolytics, depression, pain perception and overall medication consumption.

Evidence for Multidisciplinary Rehabilitation Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Hellum, 2011 (score=7.5)	Multidisciplinary Rehabilitation Program	RCT	Study funded by South Eastern Norway Regional Health Authority and EXTRA funds from Norwegian Back Pain Association. No COI.	N = 179 age 25-55 with LBP and degenerative discs for at least 1 year having tried physiotherapy or chiropractic treatment for at least 6 months without relief and score of	88 males, 91 females; Mean age for surgery group 41.1±7.1 and Rehab group 40.8±7.1.	Surgery: replace degenerative intervertebral lumbar disc with artificial lumbar disc (ProDisc II), patients not referred for post-op physiotherapy (n = 86) vs. rehab consisting of cognitive approach and supervised physical exercise for 60 hours 3-5	Follow-up 6 weeks, 3and 6 months, 1 year after treatment	Primary outcome mean±SD baseline/1 year/2 years. ODI: surgery (41.8±9.1/22.3± 17.0/21.2±17.1) vs. rehab (42.8±9.3/33.0±16.6 /30.0±16.0), p <0.001 at 1 year and p = 0.001 at 2 years. Secondary outcomes mean±SD (baseline/1 year/2 years). Back pain score: surgery (64.9±15.3/35.6±28.	"This randomised trial comparing disc prosthesis with multidisciplinary rehabilitation showed a significant difference in the primary outcome variable (Oswestry disability index after 2 years) in favour of surgery."	Most results not different. 2 year follow up.34% complications over 2 years.

				at least 30 on Oswestry disability index (ODI)		weeks that included lectures and individual discussions about anatomy, diagnostics, imaging, pain medicine, normal reactions, coping strategies, family, social life, work conditions, daily workouts to increase physical activity (endurance, strength, coordination, etc. n = 87).		6/35.4±29.1) vs. rehab (73.6±13.9/53.2± 28.4/49.7±28.4), p = 0.003 at 1 year and p = 0.009 at 2 years. SF-36 physical component summary: surgery (30.5±7.1/42.8±12.2 /43.3±11.7) vs. rehab (30.8±6.5/37.3± 11.0/37.7±10.1), p = 0.003 at 1 year and p = 0.001 at 2 years. Euro QoL (EQ-5D): surgery (0.30±0.27/0.68± 0.34/0.69±0.33) vs. rehab (0.27±0.31/0.55±0.3 2/0.63±0.28), p = 0.04 at 1 year, NS at 2 years. Self-efficacy: surgery (3.4±1.5/6.3±3.3/6. 1±2.9) vs. rehab (3.6±1.6/5.2±2.4/ 5.3±2.5), p = 0.01 at 1 year and p = 0.02 at 2 years.		
Kool, 2005 (score=8.0)	Multidisciplinary Rehabilitation Program	RCT	No industry sponsorship or COI.	N = = 174 age 20-55 with non-acute, non-specific LBP.	137 males, 37 females; Mean age 42±8.	Pain-centered (PC) treatment to reduce pain 2.5 hours a day, 6 days a week for 3 weeks (n = 87) vs. Function-centered (FC) treatment to increase work related capacity	Follow-up to 3 months.	Days at work after 3 months post-treatment: FC 25.9±32.2 vs. PC 15.8±27.5, p = 0.029. Lifting capacity change after treatment: floor-waist 2.3±5.4 vs. 0.2±3.9, p = 0.004. Perceived	"Function-centered rehabilitation increases the number of work days, self efficacy, and lifting capacity in patients with nonacute nonspecific LBP."	Data suggest pain-centered treatment inferior to function-centered over 3 months. No long-term follow-ups. Study in Switzerland and

						4 hours a day, 6 days a week for 3 weeks (n = 87).		effect after treatment: physical capacity 4.1±2.1 vs. 2.9±1.7, p <0.001; general well-being 4.0±2.1 vs. 3.1±1.9, p = 0.005; overall improvement 4.4±2.0 vs. 3.6±2.0, p = 0.009. Pain change: post treatment -0.25±2.1 vs. 0.55±1.9, p = 0.23; 3 months NS.		not clear how applicable elsewhere.
Morone, 2012 (score=6.5)	Multidisciplinary Rehabilitation Program	RCT	No sponsorship. No mention of COI.	N = 75 with chronic, non-specific LBP age 18-75	70 males, 64 females; Mean age for Surface perceptive group 52.72±17.58, back school group 55.4413.73, and for control group 57.88±12.81.	Surface for Perceptive Rehabilitation: deformable cone with small tops fixed to rigid surface that patients lie on to perform perceptive tasks to rehabilitate perception of trunk and midline 45 minute sessions 3x a week 4 weeks (n = 25) vs. Back School exercise program consisting of spine anatomy and educational intervention, exercise 10 sessions for 4 weeks (n = 25) vs. control: medical and	Follow-up 12 and 24 weeks.	VAS scale scores: baseline – surface group 6 vs. Back School 7 vs. control 7 (NS); end of treatment – surface group 4 vs. Back School 6 vs. control (p <0.001); 12 weeks – surface group 5 vs. Back School 5 vs. control 8 (p <0.001); 24 weeks – surface group 5 vs. Back School 4 vs. control 7 (p = 0.009).	"[S]urface Perceptive rehabilitation is a promising approach for pain relief in the short and long term in chronic nonspecific low back pain, whereas the Back School programme results in primarily long-term benefits."	Secondary analysis of Morone 2011. Three experimental groups. Baseline data sparse. Perceptive treatment not widely available. Control group not well described, esp. re. physical therapy or exercise. At 3 mo and 6mo, the perceptive treatment reported more pain reduction.

						pharmacological assistance, no rehabilitative exercise program (n = 25).				
Rossignol, 2000 (score=6.5)	Multidisciplinary Rehabilitation Program	RCT	Study funded by the Quebec Research Institute in Occupational Health and Safety. No mention of COI.	N = 110 workers compensated for any work-related injury to thoracic, lumbar and/or sacral portions of vertebral column, absent work for no less than 4 weeks but not more	79 males, 31 females; mean age for CORE group 36.8±9.7 and for Usual care group 38.3±10.5.	Coordination of primary health care (CORE): assisting treating physicians in finding and scheduling diagnostic and therapeutic procedures and helping coordinate health care and rehab needs between worker and Quebec Workers' Compensation Board (QWCB); nurses contacted workers weekly by phone until they returned to work to talk about back pain, functional recovery, diagnostic procedures, medical and nonmedical therapy, relations with QWCB agent, and personal problems (n = 54) vs. control –	Baseline, 3, and 6 months.	No significant differences between groups for return to work rates. Outcomes at 6 months (mean±SD): Quebec Back Pain Disability Scale (QBPDS) – CORE (20.9±22.8) vs. usual (9.1±21.4), p=0.01; Oswestry – CORE (17.2±19.7) vs. usual (7.8±17.9), p=0.02; Dallas – CORE (25.9±25.9) vs. usual (11.7±22.6), p = 0.01. Exercises in last 4 weeks (% use) at 6 months: CORE 38.6 vs. usual 20.0, p <0.05.	"The therapeutic results for workers with low-back pain could be improved by implementing the clinical practice guidelines with primary-care physicians in a large community, without delaying return to work."	Data suggest CORE program is superior

						continue with treating physician, fill out 3 and 6 month questionnaires (n = 56).				
Fairbank, 2005 (score=6.5)	Multidisciplinary Rehabilitation Program	RCT	No mention of industry sponsorship or COI.	N = 349 age 18-55 with more than 1 year of chronic LBP	172 males, 177 females; Age range of 18-55.	Spinal stabilization surgery (allowed surgeon to pick surgery) (n = 176) vs. Intensive rehab program: (outpatient daily education and exercise tailored to patients' baseline ability and included stretching of major muscle groups, spinal flexibility exercises, general muscle strengthening, spine stabilisation exercises, and cardio endurance exercise using any mode of aerobic exercise) 5 days a week for 3 weeks (n = 173).	Follow-up 6, 12, and 24 months.	Oswestry Disability Index at 24 months: surgery (34.0±21.1) vs. rehab (36.1±20.6), p = 0.045. NS between groups at 24 months for shuttle walking test, SF-36 physical component score, SF-36 mental component score, domains of SF-36 (general health perception, physical function, role limitation physical and emotional), pain, social function, mental health, and energy and vitality.	"The statistical difference between treatment groups in one of the two primary outcome measures was marginal and only just reached the predefined minimal clinical difference, and the potential risk and additional cost of surgery also need to be considered. No clear evidence emerged that primary spinal fusion surgery was any more beneficial than intensive rehabilitation."	Lack of well-defined patient criteria on entry and lack of control over surgical interventions, limiting strength of some conclusions. Data suggest no long-term differences.
Monticone, 2013 (score=6.5)	Multidisciplinary	RCT	No COI. No mention of industry sponsorship.	N = 90 diagnosed with nonspecific	38 males, 52 females; mean age for CBT 48.96±7.97	Multidisciplinary program consisting of Cognitive Behavioral	Assessments at baseline, 5 weeks, 12 months,	Outcomes (baseline/5 weeks/12 months/24 months), mean±SD.	"[O]ur findings suggest that long-lasting multidisciplinary rehabilitation is	Poor control over exact makeup of interventions.

	Rehabilitation Program			chronic LBP (>3 months), able to understand Italian, no cognitive impairments, no previous spinal surgery, deformity, infection fracture or systemic diseases, no reception of compensation for work-related disabilities, and age 18 and older.	and 49.71±7.01.	Therapy (CBT) focused on modifying fear of movement beliefs, catastrophizing thinking, and negative feelings, ensuring gradual reactions to illness behaviors, 60 minute sessions individually 1x a week for 5 weeks followed by 1 hour sessions once a month for 1 year to verify growth and reinforce self-management of dysfunctional thoughts and wrong behaviors and exercise training, multimodal motor program consisting of active and passive (manual therapy and physiological movements to improve ROM) mobilizations of spine and exercises aimed at stretching (involved groups	and 24 months.	RMDQ: multi-disciplinary (15.27± 2.94/5.04±2.04/1.31± 1.59/1.40±1.19) vs. control (15.00±2.85/11.04± 2.27/ 11.00±2.00/11.07±2.22), p <0.001. Tampa Scale for Kinesiophobia (TSK): multi-disciplinary (41.67±4.60/ 24.67±4.47/7.29±1.53/17.67±1.62) vs. control (41.78±5.06/ 40.36±5.07/ 40.33±4.55/0.96±5.17), p <0.001. Numeric rating scale (NRS): multi-disciplinary (7.02±1.07/2.69±0.97/ 1.38±1.07/1.47±1.10) vs. control (7.02±1.30/ 4.96±1.27/5.33±1.22/ 6.24±0.85) SF-36. Physical Functions (PF): multi-disciplinary (47.22±27.25/ 78.44±19.93/ 85.67±19.64/87.56± 18.35) vs. control (48.33±24.65/57.44 ±19.87/62.11±19.43 / 65.00±17.74), p <0.001. Physical Role (PR): (29.44± 35.47/72.22±28.31/	useful in changing the course of disability, fear-avoidance beliefs, pain, and QoL of patients with CLBP."	

						of lower limb and back muscles) and strengthening muscles and improving postural control (motor control of the spine and pelvis), 10-60 minute sessions 2x a week 5 weeks and twice weekly for 60 minute sessions for 1 year during which they received phone reminders (n = 45) vs. control group given only exercise (n = 45). Both programs 5 weeks (instructive phase) plus 1 year (reinforcement phase).		86.11±19.24/88.00± 17.97) vs. (31.11± 32.48/50.56± 28.94/60.33±19.14/ 2.67±17.30), p <0.001. Physical Pain (PP): (38.24± 15.36/68.36±13.97/ 78.98± 14.65/ 80.42±13.20) vs. (41.36±17.93/ 44.00±16./71 52.02±16.25/ 61.78± 13.93), p <0.001. General Health (GH): (34.00±17.72/73.22 ±18.19/ 85.00±13.81/86.33± 13.24) vs. (36.67±14.10/44.22 ±16.51/56.44±15.90 /63.11±15.01), p <0.001. Vitality (VT): (52.00± 16.93/77.22±14.71/ 90.00±11.67/91.33± 10.35) vs. (52.56± 15.36/51.89±15.85/ 55.33±11.04/56.22± 10.50), p <0.001. Social Functioning (SF): (50.83±18.34/85.83 ±15.21/ 91.00±10.47/92.33± 9.20) vs. (51.56± 17.66/63.06±17.66/ 54.44±11.35/52.50± 10.18), p <0.001. Emotional Role (ER): (39.26±35.02/76.89 ±28.90/		

								91.11±14.90/93.11±13.45) vs. (39.26±37.79/55.56±28.42/58.52±14.48/60.74±12.88), p <0.001. Mental Health (MH): (50.13±11.55/81.78±13.79/89.78±13.00/91.02±11.28) vs. (52.09±12.69/55.47±12.66/54.13±11.89/58.84±11.80), p <0.001.		
Dufour, 2010 (score=6.0)	Multidisciplinary Rehabilitation Program	RCT	Study funded by Apotekerfonden af 1999, Sygekassernes Helsefond, and the Danish National Board of Health. No COI.	N = 286 with LBP >12 weeks with or without radiating pain into legs, age 18-60.	119 males, 153 females; mean age for group A 41.2±10.0 and group B 40.6±9.1.	Group based multidisciplinary biopsychosocial rehabilitation program: treatment in groups of 6, program consisted of exercise, education, and pain management for 12 weeks and divided into 3 periods of 4 weeks (group A, n = 142) vs. intensive individual therapy assisted back muscle strengthening exercise 1 hour twice a week for 12 weeks (group B, n = 144). Assessments at baseline and 3	Follow-up at 6, 12, and 24 months.	VAS pain scores: NS between groups through study period. Roland Morris Disability Questionnaire mean±SD (3 months/6 months/12 months/24 months): Group A (3.3±5.5/3.4±6.0/4.0±5.8/3.9±6.9) vs. Group B (1.6±4.5/1.3±4.7/0.8±5.1/1.5±5.4), p = 0.001. SF-36 mean±SD (3 months/6 months/12 months/24 months): Physical functioning – Group A (12.2±21.2/10.6±22.0/12.1±24.0/11.2±23.3) vs. Group B (6.0±17.7/4.4±18.0/	"Both groups showed long-term improvements in pain and disability scores, with only minor statistically significant differences between the 2 groups."	High dropout over time. Data suggest comparable results although trends favoring multidisciplinary program.

						months after treatment.		2.0±19.0/1.6±20.4), p = 0.000; Physical component summary – Group A (5.0± 7.7/4.2±7.9/5.1±8.3 / 5.0±8.2) vs. Group B (2.8±7.3/2.2±7.7/ 1.9±7.4/1.7±7.8), p = 0.001.		
Vollenbroek-Hutten, 2004 (score=6.0)	Multidisciplinary Rehabilitation Program	RCT	No mention of sponsorship or COI.	N = 163 with chronic nonspecific LBP with no back surgery in last 3 months,	No mention of sex; mean age for treatment group 38.5±9.8 and control group 39.5±9.9	Roessingh Back Rehabilitation program (RRP): influence patient health, perceived disabilities by improving physical condition, activity level, knowledge of back problems and reducing fear of movement, 8 patients per group for 3 hours of conditional training/sport, 0.5 hours of swimming, 1.5 hours of occupational therapy, and 4 hours of physiotherapy a week for 7 weeks (n = 79) vs. usual care: no rehab treatment,	Follow-up for 6 months.	No significant differences between groups for primary outcomes of EuroQOL and the Roland Disability Questionnaire.	"The present study shows that the overall effects of a multidisciplinary treatment programme over usual care are disappointing. Only 30-50% of the patients improve as a result of such treatment and this number is not significantly different from a usual care group."	At 6mo, both groups had improved with no significant differences suggesting equal (in)efficacy. Intervention group was "Roessingh Back Rehabilitation Programme." Controls had unstructured care. Generalizability of results beyond the Netherlands is unclear.

						control group (n = 84).				
Castel 2014 (score=5.5)	Multidisciplinary Rehabilitation Program	RCT	No COI. Supported by the Foundation Marató TV3 Grant Number 070910.	N=130 patients with fibromyalgia.	130 females, 0 males. Mean age control group 49.3 years. Multidisciplinary group 47.8 years.	Conventional pharmacologic treatment (included analgesics, antidepressant, benzodiazepine and nonbenzodiazepine hypnotics) (N=61) vs. multidisciplinary treatment (CBT, and physical therapy, 24 sessions twice a week) (N=69).	3-, 6- and 12-month follow-up.	Baseline vs. 12 month follow up outcome measures control vs. multidisciplinary group of participants with BMI: ≥ 30 kg/m2: *Catastrophizing* 18.6±12.4 vs. 10.0±11.0, p<0.05. *Sleep quantity* 5.8±1.3 vs. 6.2±1.9, p<0.05.	"[T]here are not differences among normal weight, overweight and obese patients with FM regarding their response to a multidisciplinary treatment programme for FM which combines pharmacological treatment, education, physical therapy and CBT."	Significant dropout rate. Data suggest comparable efficacy between all groups in response to a multidisciplinary treatment for IM regardless of BMI.
Mangels, 2009 (score=5.5)	Multidisciplinary Rehabilitation Program	RCT	Sponsored in part by Deutsche Rentenversicherung Bund (German Annuity Insurance Association). COI, Worringen is from German Annuity Insurance Association.	N = 363 inpatients with chronic LBP and no surgeries in previous 3 months.	81 males, 282 females; Mean age traditional rehab 48.7±14.7 years, behavioral rehab 49.5±9.0 years, behavioral rehab plus booster 48.3±15.8 years.	Traditional orthopedic rehabilitation: medical care, physiotherapy, back school, and occupational therapy intended for 3 weeks, TOR, (n = 131) vs. behavioral-medical rehabilitation: traditional orthopedic treatment with psychologic treatment elements, 9 group sessions for 90 minutes	Follow-Up at 1 year.	Beck Depression Inventory, pre-post, df: TOR vs. BMR 8.03 (p <0.01); TOR vs. BMR+B 7.54 (p <0.01). Action-oriented coping, pre-post, df: TOR vs. BMR 13.03 (p <0.001); TOR vs. BMR+B 8.82 (p<0.01) – pre-follow-up: TOR vs. BMR 8.25 (p <0.01); TOR vs. BMR+B 10.27 (p <0.01). Cognitive restructuring, pre-post, df: TOR vs. BMR 8.15 (p <0.01) – pre-follow-up: TOR vs. BMR 6.22 (p	"Overall, we found both traditional and multidisciplinary inpatient pain treatment to be effective for core outcome measures."	Study of inpatient treatment that may not have generalizability outside of Germany. Data suggest similar efficacy between 3 groups, but inerventions not standardized.

						to enhance pain management skills, progressive muscle relaxation training intended for 4 weeks, BMR, (n = 113) vs. behavioral-medical rehabilitation plus booster sessions:7 additional booster sessions by phone within 12 months of discharge, BMR+B, (n = 119). Assessments at admission and discharge.		<0.01). Mental distraction, pre-post, df: TOR vs. BMR 8.86 (p<0.01); TOR vs. BMR+B 7.16 (p<0.01) – pre-follow-up: TOR vs. BMR 6.17 (p <0.05). Relaxation, pre-post, df: TOR vs. BMR 12.87 (p<0.001); TOR vs. MBR+B 19.26 (p<0.001) – pre-follow-up: TOR vs. BMR 10.18 (p <0.01); TOR vs. BMR+B 13.57 (p <0.001).		
Anema, 2007 (score=5.5)	Multidisciplinary Rehabilitation Program	RCT	No industry sponsorship or COI.	N = 196 sick listed 2-6 weeks due to non-specific LBP	116 males, 156 females; Mean age for group A 41.2±10.0 and Group B 40.6±9.1.	Workplace intervention: worksite assessments and work adjustments (n = 96) vs. usual care: Dutch occupational guidelines for LBP, education, coping with LBP (n = 100) for 8 weeks, followed by 2nd randomized trial of graded exercise for	Follow-up up to 1 year.	Time till full and lasting return to work in the graded activity group was 144 days vs. 111 days in the usual care group, p = 0.030. Total number of sick leave days during 12 month follow-up for graded activity 145 vs. 111 for usual care group, p <0.001.	"Workplace intervention is advised for multidisciplinary rehabilitation of subacute LBP. Graded activity or combined intervention is not advised."	Workplace intervention removed 43% before 2nd randomization. Time to onset of exercise 2 months after lost time began, compliance poor (65%), and exercise program structure appears variable based on wide

						those not returning to work (n = 112) start of therapy median 69 days after lost time began.				range in number of sessions indicating robust conclusions on graded exercise components not warranted. Applicability outside Netherlands unclear.
Nazzal, 2013 (score=5.5)	Multidisciplinary Rehabilitation Program	RCT	No industry sponsorship and no COI.	N = 100 age 18-65 with LBP at least 12 weeks with or without pain radiating to legs.	35 males, 65 females: Mean age group A 49.8±6.2 for group B 49.4±5.2.	Multidisciplinary biopsychosocial (Group A, n = 50) consisting of ultrasound therapy, TENS, aerobic, resistive, stretching, flexibility and postural exercises, massage, education (anatomy and pain management), and occupational therapy for 6 weeks, divided into 3 periods of 2 weeks each vs. assisted therapist exercise (Group B, N=50)	Assessments at baseline and 6 weeks. Follow-up for 12 weeks and 24 weeks.	VAS after treatment (mean± SD): Group A 4.5±1.2 vs. Group B 5.6±1.5, p = 0.0001. McGill pain scores after treatment: Group A 25.2±11 vs. 36±12.2, p = 0.0001. Oswestry disability scores after treatment: Group A 20±11.5 vs. Group B 31+ 12.8, p = 0.0001. Extension after treatment: Group A 3.9±0.6 vs. Group B 3.5±0.3, p = 0.0001. Flexion: Group A 15.2±1.2 vs. Group B 14.1±09, p = 0.0001. Right lateral bending after treatment: Group A 45.2±3.7 vs. Group B 47.9±3.0, p = 0.0001. Left lateral	"[O]ur results indicate that the combined comprehensive, and intensive multidisciplinary biopsychosocial rehabilitation management program improved spinal function and mobility measures and reduced pain scale scores."	Poor control over interventions.

						focused on back and gluteus muscle strengthening exercises for 2 hours, 5 times a week for 6 weeks.		bending after treatment: Group A 45±4.6 vs. Group B 48.2±3.4, p = 0.0001. Ability to work after treatment (n): Group A 25 vs. Group B 14, p = 0.04; after 12 weeks – Group A 27 vs. Group B 15, p = 0.02; after 24 weeks – Group A 30 vs. Group B 17, p = 0.04.		
Monticone, 2016 (score=5.5)	Multidisciplinary Rehabilitation	RCT	No COI or sponsorship.	N = 170 with non-specific chronic neck pain lasting longer than 3 months	Mean age: 53 years; 49 males, 121 females.	General exercise group (muscle strengthening, regional stretching and spinal mobilization) - one hour session of physical training each week for ten weeks, asked patients to repeat exercises at home (N = 85) vs. Multidisciplinary group (involved in group-based cognitive-behavioural therapy as well as exercises) - met with psychologist	12 months	Neck Disability Index (0-100) changes over time within and between multidisciplinary group and exercise group, respectfully: pretraining 41.9, 41.1 (time effect, group effect, and interaction effect for linear mixed model all p<0.001), posttraining 24.3, 36.7 (time effect, group effect, and interaction effect for linear mixed model all p<0.001), follow-up 21.7, 37.3 (time effect, group effect, and interaction effect for linear mixed model all p<0.001)	"A group-based multidisciplinary rehabilitation programme including cognitive-behavioural therapy was superior to group-based general physiotherapy in improving disability, pain and quality of life of subjects with chronic neck pain. The effects lasted for at least one year."	Predominantly female subjects. Data suggest group base multidisciplinary rehab which includes CBT and exercise is superior for improving disability, quality of life and pain at one year post intervention.

						once a week for one hour session for ten weeks (N = 85)				
Jay, 2016 (score=5.5)	Multidisciplinary Rehabilitation	RCT	No sponsorship and no COI.	N = 112 with chronic musculoskeletal pain.	Mean age 45.5 ± 9.0 / 476 ± 8.2 years for experimental / control groups; 0 males, 112 females.	PCMT – physical and mindfulness group-based training: supervised physical training sessions for 20 minutes four days a week, mindfulness sessions one each week for 50 minutes (N = 56) vs. REF - encouragements to follow on-going company health initiatives (N = 56)	10 weeks	Least square means difference from baseline to follow: Pain Intensity - Within group PCMT -1.5, Within group REF -0.3, Between group difference at follow-up (PCMT vs. REF) -1.0 (p<0.0001)	"A higher dose of physical-cognitive training appears to facilitate pain reduction, whereas a higher dose of mindfulness appears to increase pain."	Data suggest combining physical training with CBT and mindfulness training can significantly reduce pain.
Wong, 2011 (score=5.5)	Multidisciplinary Rehabilitation	RCT	Sponsored by a granted by the Food and Health Bureau, Hong Kong SAR Government, Hong Kong. No COI.	N = 99 with chronic pain for at least 3 months.	Aged 24 – 64 years; gender not specified, majority participants are females.	Mindfulness-Based Stress Reduction (MBSR) program consisting of a 7-hour "retreat" session (N = 51) vs Multidisciplinary pain intervention (MPI) program, educational instructions on management of chronic pain based on a self-	8 weeks	Within both the MBSR and MPI groups, there was an increases in the PCS12 at 3 months (Wald statistic = 4.62, p = 0.032) and 6 months (Wald statistic = 10.503, p = 0.001) vs baseline scores. MPI group had a statistically significant reduction in the pain related distress with a mean (SD) of 5.67 (1.88) vs. 6.12	"This randomized, clinical trial showed that both MBSR and MPI programs reduced pain intensity and pain related distress although no statistically significant differences were observed between the 2 groups and the improvements were small."	Data suggest comparable efficacy between groups and overall improvements were small.

						help book, "Managing Pain Before It Manages You" (N = 48).		(1.94) in MBSR (Wald statistic = 3.98, p = 0.046).		
Haldorsen, 2002 (score=5.5)	Multidisciplinary Rehabilitation Program	RCT	No mention of industry sponsorship or COI.	N = 654 with musculoskeletal pain	Typical participant in the study in a married woman (60%) and mean age is 43 years old.	Ordinary treatment (n = 263): referrals back to GP vs. light multi-disciplinary treatment (n = 222): 1 hour lecture (exercise, lifestyle, and fear avoidance); given individual information and feedback by team; gradually improve exercise levels despite pain vs. extensive multidisciplinary treatment (n = 169): 4 weeks of 6 hour sessions 5 days a week with CBT (group sessions 2 hours a week), education, exercise (physiotherapy daily for 1.5-3.5 hours day), and workplace interventions.	Baseline, 3, 6 and 10 months.	RTW rates 48% vs. 63% vs. 62%. Light program non-statistically better. Extensive program outperformed both arms for those patients "with a poor prognosis." Return-to- work rates were significant between light multi-disciplinary treatment vs. ordinary treatment (63% vs. 48%, p <0.02) as well as extensive multidisciplinary treatment vs. ordinary treatment (62% vs. 48%, p <0.05).	"[M]ultidisciplinary treatment is effective concerning return to work, when given to patients who are most likely to benefit from that treatment. The cost-benefit analysis of the economic returns of the light multidisciplinary and the extensive multidisciplinary treatment programs yields a positive net present social value of the treatment."	Involved disciplines were general practitioners, neurologist, psychologist, nurses and physiotherapy. Ordinary treatment/usual care provides biased comparison group ('more of same'). Data suggest either active treatment superior to usual care.

Lemstra, 2005 (5.5)	Multidisciplinary Rehabilitation Program	RCT	No mention of sponsorship or COI.	N = 79 with fibromyalgia and chronic widespread pain	Mean age for intervention group 49.7±9.57 years, control group 49.11±13.38 years; 12 males, 67 females.	Intervention group – 18 group supervised exercise therapy sessions, 2 group pain and stress management lectures, 1 group education lecture, 1 group dietary lecture, 2 message therapy sessions and rheumatologist and physical therapyist intake and discharge, all over 6 weeks (n = 43) vs control group (n = 36)	6 week post-intervention, 15 months	Reported change in health outcomes between intervention and control groups, respectively: Change in average pain intensity – 1.02±0.25, 0.22±0.20 (absolute difference between groups 0.8, p=0.019). At 15 month follow-up – (absolute difference between groups -0.21, p=0.479)	"Positive health-related outcomes in this mostly unresponsive condition can be obtained with a low-cost, group multidisciplinary intervention in a community-based nonclinical setting."	Standard care control bias. Data suggest improved perceived health status, pain intensity, disability, mood and time in both hours and minutes in pain but these interventions did not result in decreases in either prescription nor non-prescription drug use or improved work status.
Jensen, 2011 (score=5.0)	Multidisciplinary Rehabilitation Program	RCT	Study supported by Danish Working Environment Research Fund. No COI.	N = 351 age 16-60 partly or fully sick-listed from work for 4 to 12 weeks due to LBP.	168 males, 183 females; Mean age for brief intervention group 41.9±10.4 and fro multidisciplinary intervention group 42.1±10.5.	Brief intervention: seek advice about RTW; physiotherapy, increase physical activity/exercise, education, follow-up after 2 weeks (group 1, n = 175) vs. brief intervention plus multidisciplinary intervention: coordinated action plan for	Follow-up for 1 year.	Mental Health (SF-36) mean±SD after 1 year: brief intervention (70.0±20.3) vs. multidisciplinary intervention (75.0±19.8), p = 0.046. There were no other significant differences between groups.	"[A] rather limited brief intervention had the same effects on RTW, pain, disability, and self-rated health as a more comprehensive multidisciplinary intervention."	Secondary analyses of Jensen C, Jensen OK, Christiansen DH, Nielsen CV:

						RTW; interview with case manager 1-2 hours to discuss work history, private life, and pain and disability perception; created tailored rehab program together for partial or full RTW (n = 176).				
Skouen, 2002 (score=5.0)	Multidisciplinary Rehabilitation Program	RCT	No mention of industry sponsorship. COI category stated as 14. Interpretation not included.	N = 195 with LBP age 21-66 years.	69 males, 126 females; Mean age of 44.0±11.7.	Control: (n = 86) treatment as usual with 31 men, and 55 women. vs. Light Multidisciplinary (LMT): (n = 52) 21 men, and 31 women Vs. Extensive Multidisciplinary (n = 57) 17 men, and 40 women.	Follow-up at 12, 18 and 24 months.	Significant results in men for Light Multidisciplinary vs. control group. At 12-months; mean = 5.1, SD = 4.7 for control, and mean = 7.9, SD = 4.7 for LMT with p = 0.03. At 18-months; mean=8.1, SD = 7.0 for control, and mean = 12.5, SD = 5.9 for LMT with p = 0.02. At 24-months; mean = 11.1, SD = 9.6 for control, and mean = 16.9, SD = 7.5 for LMT with p = 0.02 for men. Women had no significant results between groups.	"The challenge of the future may be to offer at risk patients, at approximately 8 weeks absence from work, a light multidisciplinary treatment program at a multidisciplinary spine clinic. Our light multidisciplinary treatment model seems appropriate for men. In women, however, the emphasis on illness behavior, family situation, and job factors, such as control over work and job satisfaction, may be important elements in future LBP programs, but this should be	Post-hoc sub-analysis of larger RCT.

									further evaluated."	
Von Korff, 2005 (score=5.0)	Multidisciplinary Rehabilitation Program	RCT	Sponsored by a grant from the National Institutes of Health. No mention of COI.	N = 317 with back pain (mainly chronic) and 7+ activity limitation on 23-item Roland Disability Questionnaire (RDQ).	90 males, 150 females; Mean age for intervention group 49.7±9.0 and for the control group 49.8±9.8.	Intervention group: 4 in person visits with psychologist and physical therapist focusing on back pain fear, exercise plans and goals, relaxation and pain management (n = 119) vs. control group: usual care consisting of pain medications, primary care visits, and ancillary services such as physical therapy (n = 121).	Follow-up at 2, 6, 12, and 24 months after randomization.	Mean±SD RDQ baseline/24 months, intervention vs. control: 12.3±5.5/ 8.1±6.5 vs. 11.4±5.7/9.1±7.2 (p = 0.0078). Mean±SD worrying rate baseline/24 months, intervention vs. control: 6.7±2.6/3.5±3.0 vs. 6.2±2.7 /4.5±3.2 (p <0.0001). Mean±SD fear avoidance baseline/24 months, intervention vs. control: 41.1±8.8/ 34.3±9.7 vs. 41.3±8.2/ 38.4±9.9 (p = 0.0001). Mean±SD pain intensity baseline/24 months, intervention vs. control: 5.7±1.8/ 4.3±2.1 vs. 5.8±1.8/ 4.6±2.5 (NS). Percent with clinically meaningful reduction in RDQ intervention vs. control: 2 mo 27.7 vs. 13.2 (p = 0.0007); 6 months 42.2 vs. 23.7 (p = 0.0005); 12 months	"[A]n intervention integrating fear reducing and activating interventions into care for chronic back pain patients produced sustained reductions in patient fears, commonly activity limitations related to back pain, and days missed from usual activities due to back pain."	Baseline differences in pain/limitations (e.g., 43.6% vs. 28.9% severe activity limitations) raising question of randomization failure. At 2 yrs, the interventional group had less fear, less pain and less activity limitations. High dropout rate at 2yrs.

								44.6 vs. 22.7 (p = 0.03); 24 months 49.4 vs. 37.0 (p = 0.08).		
Monticone, 2016 (score=5.0)	Multidisciplinary Rehabilitation	RCT	No mention of industry sponsorship or COI.	N = 150 with chronic low back pain (CLBP).	Mean age 53.2 (11.1) / 53.8 (10.4) for experimental / control groups; 58 males and 91 females.	Experimental group: 2 physiatrists, a psychologist, and 4 physiotherapists, plus exercise (N = 75) vs Control group: task oriented exercise, group based CBT (N = 75).	5-weeks, 12 and 24 months	Oswestry Disability Questionnaire (ODI): baseline vs post-treatment score for both groups favoring experimental group, (p < 0.001). Effect of time / group / and time by group: p < 0.001 / p < 0.001 / and p < 0.001.	"This light group-based multidisciplinary cognitive behavioural rehabilitation programme was superior to traditional exercises in reducing disability, kinesiophobia, catastrophizing, and enhancing the quality of life of subjects with CLBP."	Usual care control bias. Data suggest disability decreased in group based multidisciplinary CBT rehab group as well as improved kinesiophobia, quality of life, and less catastrophizing.
Tavafian, 2011 (score=5.0)	Multidisciplinary Rehabilitation Program	RCT	No industry sponsorship or COI.	N = 197 with chronic LBP	43 males, 154 females; Mean age of intervention group 44.6±10.2 and control group 45.9±11.3.	Intervention Group receiving group based multidisciplinary rehabilitation program plus oral medication (n = 97) vs. Control group receiving oral medication (n =100).	Follow-Up of 6 months.	Significant difference on all SF-36 subscales within each group by time (p <0.01), except mental health (p = 0.7). Mean±SD for QDS scores at baseline comparing intervention group vs. control group at baseline: 35.45±20.19 vs. 33.08±19.69; and 6 months follow-up: 18.65±16.14 vs. 27.19±17.85 (p = 0.01). Mean±SD RDQ scores comparing intervention group vs. control group at	"This study revealed that the multidisciplinary rehabilitation program added to a typical oral medication regimen can improve QOL and disability of patients with CLBP in a 6-month period of follow-up."	Unclear how blinding occurred. Contact time bias. Data suggest possible modest efficacy.

								baseline: 9.80±5.07 vs. 10.04±5.28; and at 6 months follow-up: 7.03±5.49 vs. 8.80±5.68.		
Jensen, 2012 (score=5.0)	Multidisciplinary Rehabilitation Program	RCT	Study supported by Danish Working Environment Research Fund. No COI.	N = 351 age 16-60 partly or fully sick-listed from work for 3 to 16 weeks due to LBP	168 males, 183 females; Mean age for brief intervention group 41.9±10.4 and fro multidisciplinary intervention group 42.1±10.	Brief intervention: seek advice about RTW; physiotherapy, increase physical activity and exercise, and education, follow-up after 2 weeks (group 1, n = 175) vs. brief intervention plus multidisciplinary intervention: coordinated action plan to facilitate RTW; interview with case manager for 1-2 hours to discuss work history, private life, and pain and disability perception; created tailored rehab program together for partial or full RTW (n = 176).	Follow-up for 2 years.	No significant differences between groups.	"The effects of the brief and multidisciplinary interventions at the two-year follow-up were similar to the effects reported at the one-year follow-up."	Secondary analyses of Jensen C, Jensen OK, Christiansen DH, Nielsen CV:
van Eijk-Hustings, 2013 (score=4.5)	Multidisciplinary	RCT	No COI. Sponsored by Maastricht University Medical Centre	N = 203 with fibromyalgia based on the American	Mean age for those in MD who started program	Multidisciplinary intervention with aftercare, two phase program with	21-24 months	Intention-to-treat analyses among the MD group showed improvements within and small	"MD seemed to yield positive effects, but firm conclusions with regard to	Usual care bias. Conclusions are limited due to unequal participation and

	Rehabilitation Program		and by Care Renewal Grants of medical insurance companies in region.	College of Rheumatology criteria	41.6±8.8, MD who did not start 41.3±11.0, those in AE who started 43.9±7.6, AE who did not start 39.1±9.6, UC 42.9±11.0; 55 males, 148 females.	12-week course consisting of 3 half days each week, focusing on sociotherapy, physiotherapy, psychotherapy and creative arts therapy with group interaction (MD) (n = 108) vs. Aerobic exercise (AE), twice per week (n = 47) vs. Usual care (UC) (n = 48)		differences between groups at follow-up. Between MD and UC group a not statistically significant difference as follow-up was found (difference between groups 0.22, 95% CI -0.12-0.56).	effectiveness cannot be formulated due to small between-group differences and limitations of the study."	completion rates between groups (AE group had significant dropout).
Lindström, 1992 (score=4.5)	Multidisciplinary Rehabilitation Program	RCT	No mention of industry sponsorship or COI.	N = 103 with subacute LBP off work for 6 weeks	71 males, 32 females; mean age in activity group 39.4±10.7 and control group 42.4±10.9	Graded activity group (n = 51) vs. controls: no treatment (n = 52) for 1 year. Graded activity group with measured functional capacity (mobility, strength and fitness), workplace visit, back school education, and an individual, submaximal gradually increased exercise program with operant conditioning.	Follow up at one year.	Increases in arm strength, abdominal muscle strength, back muscles, and many other outcome measures preserved at 1 year in activity group. Activity group RTW 5.1 weeks earlier, p = 0.03.	"The patients with subacute, nonspecific, mechanical LBP who participated in the graded activity program regained occupational function faster than did the patients in the control group, who were given traditional care."	Involved orthopedic surgery and physiotherapy. GPs administered routine care, but not otherwise involved. Social worker performed psychosocial screening. Graded activity program reduced long-term sick leave especially in males. Intensive exercises, work-hardening exercises, or expensive equipment not necessary to regain

										occupational function.
Haldorsen, 1998 (score=4.5)	Multidisciplinary Rehabilitation Program	RCT	Study funded by Royal Norwegian Department of Health and Social Affairs. COI: Skouen.	N = 573 (223 with back pain) sick-listed 8 weeks due to muscle pain and currently employed	171 males, 298 females; Mean age of 43±10.6.	Multi-disciplinary rehabilitation program 6 hour sessions 5 days a week for 4 weeks – physical treatment, cognitive behavioral modification, education, and workplace-based interventions (Treatment group, n = 312; n = 142 with back pain) vs. follow-up by GP without feedback or advice on therapy (Control group, n = 157; n = 81 with back pain) Treatment for 4 weeks, Patients given pre and post-test.	Follow-up at 2 months, 6 months, and 10 months.	No significant differences between groups for RTW rate. Outcomes at post-test (mean±SD): regular physical training – treatment 3.1±0.9 vs. control 2.5±1.1, risk ratio 2.02; work satisfaction – treatment 3.1±1.1 vs. control 2.71.1, risk ratio 1.54; attribution style – treatment 17.1±5.3 vs. control 18.0±6.4, risk ratio 1.66; psychological distress – treatment 35.4±10.3 vs. 36.9±9.9, risk ratio 1.61; subjective health complaints – treatment 16.7±10.7 vs. control 17.4±10.4, risk ratio 1.22; Pain (VAS, afternoon) – treatment 48.2±27.4 vs. control 52.1±28.9, risk ratio 1.31.	"[T]he patients did not return to work at a higher rate than those receiving ordinary treatment available through the general practitioners at one year follow-up."	Significant change in contact time between groups.
Henchoz, 2010 (score=4.5)	Multidisciplinary Rehabilitation Program	RCT	No industry sponsorship or COI.	N = 105 with subacute to chronic LBP, phases 2 to 6	64 males, 41 females; Mean age for Multidisciplinary group 41.09±10.6	Functional multi-disciplinary rehab (FMR, n = 49) for 5-7 hours per day, 5 days a week, for	Follow up of 1-year.	Beginning of FMR/End of FMR mean (SD) for Shirado test (s) for exercise program 54.46 (47.51)/66.13 (45.95), p <0.01; for	"A favorable long-term outcome was observed after functional multidisciplinary rehabilitation in both patient	Data suggest no meaningful differences in outcome measures between groups

				of Krause classification.	and fro routine group 39.25±9.05 .	3-weeks vs. Exercise program (n = 56) sessions lasted 90 min.		routine follow-up 42.79 (30.34)/65.45 (41.86), p <0.001. Sörensen tests (s) for exercise program 46.44 (40.97)/64.82 (49.83), p <0.001; for routine follow-up 38.09 (36.65)/67.12 (50.63), p <0.001, MMS test, extension (cm) for exercise program -1.4 (0.89)/-1.63 (0.78), p<0.05; for routine follow-up -1.33 (0.73)/-1.46 (0.7), p=0.127. Fingertip-floor distance (cm) for exercise program 17.56 (15.91)/11.32 (13.13), p <0.001; for routine follow-up 21.6 (18.59)/17.31 (18.44), p<0.001. Modified Bruce test (min) for exercise program 9.81 (2.31)/11.23 (2.20), p <0.001; for routine follow-up 53.24 (18.27)/37.45 (21.73), p <0.001. Back pain VAS (%) 53.24 (18.27)/37.45 (21.73), p <0.001; for routine follow-up 51.56 (21.54)/35.93	groups. Patients who participated in an exercise program obtained some additional benefits."	at same time point. Both groups improved over time.

								(23.67), p <0.001. SFS (0-200) for exercise program 114.16 (40.8)/126.53 (32.08), p <0.01; for routine follow-up 109.69 (37.36)/129.12 (37.85), p <0.001.		
Monticone, 2014 (score=4.5)	Multidisciplinary Rehabilitation	RCT	No sponsorship and no COI.	N = 20 with chronic low back pain (CLBP).	Mean age 58.9 ± 16.4 / 56.6 ± 14.4 for experimental / control groups; 9 males and 11 females.	Experimental group included stabilizing exercises plus usual-care rehabilitation (N = 10) vs Control group, 60 minutes cognitive-behavioral sessions once a week (N = 10).	8 – weeks	Disability improvement by 61 % in the experimental vs 25 % in the control group, a significant effect of time (p < 0.001), group (p = 0.027), and time-by-group interaction (p = 0.001) in favor of the experimental group.	"The multidisciplinary rehabilitation programme including cognitive–behavioural therapy was superior to the exercise programme in reducing disability, kinesiophobia, catastrophizing, and enhancing the quality of life and gait cadence of patients with CLBP."	Pilot study. Small sample, usual care control bias. Data suggest multidisciplinary rehab group which included CBT was better for improving disability, kinesiophobia, gait cadence, castrophizing, and quality of life.
Jellema, 2005 (score=4.5)	Multidisciplinary Rehabilitation Program	RCT	No industry sponsorship or COI.	N = 62 with non-specific LBP of less than 12 weeks	42 males, 18 females; Mean age for minimal intervention group 43.0±7.2 and usual care group 45.7±7.4.	Minimal intervention strategy (n = 30) vs. Usual care (n = 32).	Follow up at 6, 13, 26, and 52 weeks.	No significant difference between groups.	"This study provides no evidence that (Dutch) general practitioners should adopt our new treatment strategy aimed at psychosocial prognostic factors in patients with (sub)acute low back pain."	Cluster randomization results in significant differences in numbers or participants in each treatment arm.

Kääpä 2006 (score=4.0)	Multidisciplinary Rehabilitation Program	RCT	No COIs or industry sponsorship.	N = 120 females age 22-57 years old, employed as health care and social care professionals with nonspecific chronic LBP	Mean age: 46.25 Sex: 0 males, 120 females.	Multi-disciplinary restoration group or MR; 8-week intervention, 70 hours rehab program, including intensive period of 5 days (6 hours per day), home-training of 2 weeks, and semi-intensive period of 5 weeks. (n = 59) vs. Individual Physiotherapy group or IP, 10 1-hour treatment sessions of 6-8 weeks. Sessions included 30- to 40-minute passive pain treatment and 15-20-minute light active exercise (n = 61).	6, 12, and 24 months	No significant differences between groups with respect to LBP intensity, sciatic pain intensity, back specific disability, subjective working capacity, sick leave due to back pain, beliefs of working ability about 2 years, and symptoms of depression at any time during study. Significant difference between groups with respect to General Well Being after rehabilitation (MR: 7.74 ± 5.45 vs. IP: 9.83 ± 5.4, p = 0.02)	"The results of this study indicate that semilight outpatient multidisciplinary rehabilitation program for female chronic low back pain patients does not offer incremental benefits when compared with rehabilitation carried out by a physiotherapist having a cognitive-behavioral way of administering the treatment."	Data suggest comparable efficacy between treatment groups and positive effect maintained at 2 years. Primary reliance on passive methods in individualized physiotherapy group may have resulted in these findings.
Campello, 2012 (score=4.0)	Multidisciplinary Rehabilitation Program	RCT	Study sponsored by Navy & Marine Corps Public Health Center (NMCPHC), funded by Office of Assistant Secretary of the Army for Installations and	N = 33 active duty service members for all US military branches seeking care for non-specific LBP interfering	30 males, 3 females; Mean age for BTW 33.1±6.6 and for usual care 32.0±7.2.	Multidisciplinary program – Backs to Work (BTW): coordinated multi-disciplinary, reconditioning program 3 hours a day, 3 days a week 4 weeks. BTW goal-	Follow-up at 12 weeks.	Oswestry score (baseline/4 weeks) mean±SD: control (24.3±10.5/21.0±8.3) vs. BTW (24.5±7.7/10.7±6.5, p = 0.014.	"This feasibility study was successful in demonstrating the implementation and execution of an early intervention multidisciplinary program for Navy	Small sample size (N=33). Pilot Study.

			Environment – OASA (I&E), and managed by Battele. No mention of COI.	with normal work or life for 4-12 weeks.		oriented program of aerobic conditioning, strength training, flexibility exercises. Cognitive behavioral treatment included education on psychosocial variables that affect pain, relaxation training, modification of maladaptive beliefs, and problem solving (n = 16) vs. standard of care at a US Navy Military Treatment Facility (MTF) – treatment at the discretion of their doctor 2-3x a week up to 1 hour and included any of following: ultrasound, heat, ice, and electrical stimulation, traction, exercises, back class, and spinal			personnel with NSLBP."	

						manipulation (n = 17).				
Loisel, 1997 (score=4.0)	Multidisciplinary Rehabilitation Program	RCT	No mention of industry sponsorship or COI.	N= 130 with back pain.	62 males, 42 females; Mean age for usual care 41.7±10.0, clinical care 40.2±8.5, Occupational care 44.5±5.7, and Full care 37.4±8.1.	Usual care (n = 26) vs. Clinical intervention: involved after 8 weeks absence visit to "back pain specialist," back care school, after 12 weeks absence, multidisciplinary work rehab intervention (n = 31) vs. Occupational intervention: after 6 weeks absence, visit to OT, ergonomics evaluation (n = 22) vs. Full intervention (combination of last two, n = 25).	Follow-up at 12, 24 and 52 weeks.	RTW rate 2.23 times greater in occupational intervention group vs. usual care, p = 0.04. Median duration of work absence was 60 days for full intervention, 67 for occupational intervention, 131 for clinical intervention, and 120.5 days for usual care group, p = 0.01 for occupational effect groups vs. 2 groups without intervention.	"Close association of occupational intervention with clinical care is of primary importance in impeding progression toward chronicity of low back pain."	Involved disciplines were occupational physicians, ergonomists, "back specialists," and apparently physiotherapists. Long times off work atypical for U.S. and unclear if results generalizable outside the Netherlands.
Henchoz, 2010 (score=4.0)	Multidisciplinary Rehabilitation Program	RCT	No mention of industry sponsorship or COI.	N = 105 with subacute or chronic LBP without irritative neurological deficit and Krause classification phases 2-6.	64 males, 41 females; Mean age for EP group 41.1±10.6 and UC group 39.3±9.1.	Exercise program (EP, n = 56): 24 group training sessions 12 weeks 90 minute submaximal exercises under supervision vs. usual care (UC, n = 49): advised to exercise regularly and written description of exercises used during FMR	Assessments at end of FMR and 1 year after end of EP/UC.	No significant differences between groups.	"[A]dding an exercise programme after FMR compared with usual care does not offer significant long-term benefits in terms of quality of life and direct and indirect costs."	Much missing data, especially OP group. Baseline differences including better fitness in MDRP group, possible moderate randomization failure. As all of work <6mo, likely had PT, which would bias in favor of

						continued at home after both groups received functional multi-disciplinary rehab (FMR): 3-week outpatient program, groups of 5 patients treated Monday-Friday for 5-7 houra day with exercises, ergonomics, 1-to-1 and group psychosocial interventions, relaxation therapy and information, individually tailored pharmacotherapy and regular follow-up.				other treatment. Data favor MDRP.
Eisenberg, 2012 (score=4.0)	Multidisciplinary Rehabilitation Program	RCT	Study supported in part by grants from National Center for Complementary and Alternative Medicine and Bernard Osher Foundation. No COI.	N = 20 age 18-70 undergoing evaluation for work or non-work related LBP for 21-84 days (subacute) and >3 on 0-10 scale in past week	9 males, 11 females; Mean age of integratred care 47.2±9.1 and for usual care 48.0±8.0.	Integrative care plus usual care: acupuncture, chiropractic, internal medicine consultation and referral, massage therapy, occupational therapy, physical therapy, mind-body techniques, neurology	Follow-up by phone at 2, 5, 12, and 26 weeks.	Bothersomeness at week 12 (mean±SD): IC (1.4±2.8) vs. UC (5.7±3.6), p = 0.02. Pain at week 12: IC (0.6±1.2) vs. (5.0±3.7), p=0.005. Pain at week 26: IC (1.0±1.6) vs. US (4.7±3.9), p = 0.04. Worst activity at week 12: IC (3.1±3.4) vs. US (6.7±3.7), p=0.03. SF-12 Physical at week 26: IC	"It is feasible for a multidisciplinary, outpatient IC team to deliver coordinated, individualized intervention to patients with subacute LBP. Results showed a promising trend for benefit of treating patients with persistent LBP with this IC model, and warrant evaluation	Small sample size. Alternative and usual care are ill defined.

						consultation, nutritional counseling, orthopedics consultation, and psychiatry and rheumatology consultation and referrals up to 2 times a week up to 12 weeks (IC, n = 14) vs. usual care only: consisting of NSAIDs, muscle relaxants, as-needed referral to physical therapy, limited bed rest, education, and activity alterations. (UC, n = 6)		(51.0±8.9) vs. UC (43.8±13.1), p = 0.03.	in a full-scale study."	
Keller, 1997 (score=4.0)	Multidisciplinary Rehabilitation	RCT	No mention of industry sponsorship or COI.	N = 64 with chronic LBP (Quebec Task Force), no prior pain management program, able to attend, and fluent in German.	Mean age 46.89 (12.25) and 49.10 (12.75) for treatment and control groups; 18 males and 45 females.	Treatment program, included group meetings and 18 individualized sessions supervised by physicians, physiotherapists, and pain psychologist, education and relaxation exercises included (N = 35) vs	6 months	Pain frequency, typical pain intensity and disability were reduced. Strength and endurance not affected. Most changes maintained at follow-up.	"These changes corresponded with improvements in well-being, whereas depression scores remained unchanged as before."	Wait-listed controls biases in favor of intervention. Baseline characteristics sparse and suggest trends towards differences. Co-interventions not well described. Data suggest physical activity

						Wait-list controls (N = 29).				improves outcomes in chronic LBP. Exercise components are not well described, but appear to emphasize posture.

Evidence for Interdisciplinary Pain Rehabilitation Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Staal 2004 (score = 8.5)	Interdisciplinary Pain Rehabilitation	RCT	By the Dutch Health Insurance Executive Council (CVZ). No COI.	N = 105 with subacute LBP (median 8 to 8.5 weeks duration, range 6-14 weeks) among airline employees	126 males, 8 females; Mean age graded activity 39±9, Usual Care 37±8.	Behavioral-oriented, graded exercise therapy vs. heterogeneous usual care. Intervention bi-weekly 1-hour exercise with physiotherapists who emphasized operant conditioning principles, focusing on achieving goals to improve function. Specific exercises (aerobic, abdominal,	Baseline, 3 and 6 months.	At 6 months, pain ratings not significantly different, but improved more in graded exercise. Functional status at 6 months: graded activity (7.8±6.6) vs. usual care (6.4+6.6), p = 0.11. Pain at 6 months: graded activity (2.9±3.1) vs. usual care (2.7±2.8), p >0.2. Hazard ratio for period up to 50 days after randomization 1.0 and 1.9 for period from 50 days after randomization favored graded activity.	"Graded activity was more effective than usual care in reducing the number of days of absence from work because of low back pain."	Despite high-quality score on grading, due to inclusion of multiple research study design techniques, article was so heterogeneous that firm conclusions are not warranted.

						back, leg, individually tailored) to "simulate and practice problematic tasks at work or problematic activities of daily living." Sessions continued until subjects RTW or 3 months passed.				
Kool 2005 (score = 8.0)	Interdisciplinary Pain Rehabilitation	RCT	Supported by the Swiss Federal Office of Health. No COI.	N = 174 age 20-55 with non-acute, non-specific LBP	137 males, 37 females; Mean age 42±8.	Pain centered treatment to reduce pain 2.5 hours a day 6 days a week for 3 weeks (n = 87) vs. function-centered treatment to increase work-related capacity 4 hours a day 6 days a week for 3 weeks (n = 87).	Baseline and 3 month follow up	Days at work after 3 months post-treatment: function 25.9±32.2 vs. pain centered 15.8±27.5, p = 0.029. Self efficacy change (PACT) after treatment: function 5.9±32.5 vs. pain centered -7.4±4.4, p = 0.003. Perceived effect after treatment: physical capacity 4.1±2.1 vs. 2.9±1.7, p <0.001; overall improvement 4.4±2.0 vs. 3.6±2.0, p = 0.009. Pain change: post-treatment: 0.25±2.1 vs. 0.55±1.9, p = 0.23.	"Function-centered rehabilitation increases the number of work days, self efficacy, and lifting capacity in patients with nonacute nonspecific LBP."	Study in Switzerland. Not clear how applicable to U.S.
Fairbank 2005 (score = 6.5)	Interdisciplinary Pain	RCT	The Medical Research Council supported the trial financially	N = 349 with chronic LBP at least 1 year duration),	162 males, 177 females;	Lumbar spine fusion (n = 176) vs. intensive rehabilitation (n	Baseline, 6, 12, and 24 months.	The 48 patients randomized to conservative care later opted for	"No clear evidence emerged that primary spinal fusion surgery was	A weakness of this study is the lack of well-

	Rehabilitation		and was represented on the steering committee. Authors have received funding from Synthes for a spinal fellow.	considered to be a surgical candidate, and thought to not have exclusions such as psychiatric issues	Age range 18-55.	= 173): intensive rehabilitation program consisted of education and exercise full time for 3 consecutive weeks, followed by 1 full day of follow-up at 1, 3, 6, and 12 months. Exercises were individualized, graded, and consisted of endurance, stretching, flexibility, strengthening and aerobics.		surgery; 7 surgery patients opted for conservative care; 55.1% fusion patient's required further treatment after allocated treatment vs. 39.3% rehab group, 19 surgical cases incurred complications; 11 required additional surgery. Both groups reported reductions in disability during 2 years of follow-up, "possibly unrelated to the interventions." Oswestry disability index at 24 months: surgery (34.0±21.1) vs. rehab (36.1±20.6), p = 0.045. NS between groups all other outcome measures.	any more beneficial than intensive rehabilitation."	defined patient criteria on entry and lack of control over surgical interventions, which limits strength of some conclusions and generalizability.
Haldorsen 2002 (score = 5.5)	Interdisciplinary Pain Rehabilitation	RCT	This work was financed by a grant from the Royal Norwegian Department of Health and Social Affairs to Department of Health and Social Welfare. No mention of COI.	N = 654 with musculoskeletal pain	Majority female (Not specified); Mean age of 43.	Ordinary (n = 263): referred backed to GP vs. light multi-disciplinary treatment (n = 222): 1-hour lecture on exercise, lifestyle, fear avoidance; given individual feedback and information by	Baseline, 14 month follow-up.	Return-to-work rates 48% vs. 63% vs. 62%, thus light program non-statistically better. Extensive program outperformed other two arms for those patients "with a poor prognosis." Patients that gave poor results return to work rate was significant both	"Multidisciplinary treatment is effective concerning return to work, when given to patients who are most likely to benefit from that treatment. The cost-benefit analysis of the economic returns of the light	Involved disciplines were general practitioner, neurologist, psychologist, nurse, and physiotherapy.

						team; vs. extensive multi-disciplinary treatment (n = 169): 4 weeks of 6-hour sessions 5 days a week with cognitive behavioral modification (in group sessions 2 hours a week), education, exercise (physiotherapy daily for 1.5-3.5 hours a day), and workplace interventions.		between light multidisciplinary treatment and ordinary treatment ($p < 0.02$) and between extensive multidisciplinary treatment and ordinary treatment, $p < 0.05$.	multidisciplinary and the extensive multidisciplinary treatment programs yields a positive net present social value of the treatment."	
Anema 2007 (score = 5.5)	Interdisciplinary Pain Rehabilitation	RCT	Supported by federal funds. No COI.	N = 196 sick listed 2 to 6 weeks due to nonspecific LBP	129 males,	Workplace intervention: worksite assessments and work adjustments (n = 96) vs. usual care: Dutch occupational guidelines for LBP, education, coping with LBP (n = 100) for 8 weeks, followed by a second randomized trial of a graded exercise protocol among patients who did not return to work based on the workplace intervention (n	Follow-Up at baseline, 12. 26, and 52 weeks.	Graded activity had negative effect on return to work.	"Workplace intervention is advised for multidisciplinary rehabilitation of subacute LBP. Graded activity or combined intervention is not advised."	Workplace intervention performed first, removing 43% of subject population prior to 2nd randomization, time to onset of exercise approximately 2 months after lost time began, compliance poor (65%), exercise program structure highly variable based on wide range in number of

						= 112) start of therapy median 69 days after lost time began with follow-up up to 1 year.				sessions indicating that robust conclusions on graded exercise components of study not warranted.
Amris 2014 (score=5.5)	Interdisciplinary Pain Rehabilitation	RCT	Sponsored by grants from The Oak Foundation, Schioldanns Fond, and The Danish Rheumatism Association. No COI.	N= 191 patients diagnosed with Chronic Widespread Pain (CWP) accord to the 1990 American College of Rheumatology criteria.	0 males, 191 females; Mean age for intervention group 44.4±10.9 and control group 44.2±10.8.	Intervention group (N =96) received 2 weeks of multicomponent treatment, every day for 3-5 hours. vs Control Group (N =95) A controlled wait list group.	Baseline and 6 months.	Assessment of Motor and Process Skills (AMPS) ADL motor logits, baseline to 6 mo change, rehab group (95% CI) vs control group (95% CI) & group difference (p-value): 0.23 (0.15-0.31) vs 0.02 (-0.05-0.10) & .20 ((0.09-0.31) (p=0.0003)). AMPS ADL Process logits, baseline to 6 mo change, rehab group (95% CI) vs control group (95% CI) & group difference (p-value): 0.07 (0.02-0.12) vs -0.13 (-0.18 - -0.08) & .20 ((0.12-0.27) (p<0.0001)).	"We conclude that even in fibromyalgia patients presenting with a longstanding, substantial disability, the 2-week group-based multicomponent treatment course resulted in observable improvements of functional ability in a subgroup of patients at 6-month follow-up. This improvement, however, was not reflected in patient-reported outcomes, including self-reported functional ability on standardized questionnaires."	Waitlist control bias. At 6 months, a subgroup of the intervention group reported functional improvement. Unblinded study. Data suggest there was an observed functional improvement in interdisciplinary rehab group but this was not reported by the patients themselves.
Jensen 2005 (score = 5.0)	Interdisciplinary Pain Rehabilitation	RCT	Sponsord by AFA Insurance and Alecta Insurance. No mention of COI.	N = 214 with non-specific chronic spinal pain	97 males, 117 females; males mean age	Behavior-oriented physiotherapy (PT, n = 54): 20 hours a week;	Baseline, and 3 years	Behavior-oriented physiotherapy (PT), cognitive behavioral therapy (CBT), physiotherapy and	"[A] full-time behavioral medicine programme (PT and CBT) is a cost-	Involved were physicians, physiotherapists

					97±11, females mean age 42±10.	individual training program had goal setting, improved muscular endurance, aerobic training, pool training, relaxation techniques, and body awareness therapy vs. cognitive-behavioral therapy (CBT, n = 49): 13-14 hours a week of activity planning and goal setting, problem solving, applied relaxation, cognitive coping techniques, distracting imagery, etc. vs. physiotherapy and cognitive-behavioral therapy full time (BM, n = 63) vs. treatment-as-usual (TU, n = 48) control of routine health-care, no intervention; 5 assessments over 3 years.		cognitive behavioral therapy (PT/CBT), and treatment-as-usual (TU) control in Sweden. Required to be sick-listed 1-6 months. Interventions lasted 4 weeks, groups of 4-8 patients. All showed marked reductions in sick leave. Total absences reduced more in PT and CBT, followed by CBT, followed by PT. Total costs lower in PT and CBT. BM group used physiotherapists less than others (p = 0.05). Control group used social services less than intervention groups, p = 0.05.	effective method for improving health and increasing return to work in women working in blue-collar or service/care occupations and suffering from back/neck pain."	, and psychologists.

Lindström, 1992 (score=4.5)	Interdisciplinary Pain Rehabilitation	RCT	No mention of industry sponsorship or COI.	N = 103 with subacute LBP off work for 6 weeks	71 males, 32 females; mean age in activity group 39.4±10.7 and control group 42.4±10.9	Graded activity group (n = 51) vs. controls: no treatment (n = 52) for 1 year. Graded activity group with measured functional capacity (mobility, strength and fitness), workplace visit, back school education, and an individual, submaximal gradually increased exercise program with operant conditioning.	Follow up at one year.	Increases in arm strength, abdominal muscle strength, back muscles, and many other outcome measures preserved at 1 year in activity group. Activity group RTW 5.1 weeks earlier, p = 0.03.	"The patients with subacute, nonspecific, mechanical LBP who participated in the graded activity program regained occupational function faster than did the patients in the control group, who were given traditional care."	Involved orthopedic surgery and physiotherapy. GPs administered routine care, but not otherwise involved. Social worker performed psychosocial screening. Graded activity program reduced long-term sick leave especially in males. Intensive exercises, work-hardening exercises, or expensive equipment not necessary to regain occupational function.
Loisel 1997 (score = 4.0)	Interdisciplinary Pain Rehabilitation	RCT	Supported by a grant from the Institut de la Recherche en Sante at Securite du Travail du Quebec, Canada. No mention of COI.	N = 130 with back pain	69 males, 32 females; Mean age usual care 41.7±10.0, clinical 40.2±8.5, occupational 44.5±5.7, full 37.4±8.1.	Usual care (n = 26) vs. clinical intervention (after 8 weeks absence): visit to "back pain specialist," back care school after 12 weeks absence, multi-disciplinary	Baseline and 1 year follow up.	Return-to-work rate 2.23 times greater in occupational intervention group vs. usual care, p = 0.04. Median duration of work absence was 60 days for full intervention, 67 for occupational	"Close association of occupational intervention with clinical care is of primary importance in impeding progression toward chronicity of low back pain."	Involved disciplines were OM physicians, ergonomists, "back specialists," and apparently physiotherapists.

						work rehab (n = 31) vs. occupational intervention after 6 weeks absence, occupational therapist visit, ergonomic evaluation (n = 22) vs. full intervention (combination of last two) (n = 25); follow-up 12 and 24 weeks and 1 year.		intervention, 131 for clinical intervention, and 120.5 days for usual care, p = 0.01 for occupational effect groups vs. 2 groups without intervention.		
Becker 2000 (score = 4.0)	Interdisciplinary Pain Rehabilitation	RCT	No mention of sponsorship or COI.	N = 189 with chronic non-malignant pain	59 males, 108 females; Mean age in group MPT 57.7±15.8, in group GP 55.1±14.6, in group WL 57.2±15.5.	Outpatient multi-disciplinary pain centre treatment: cognitive behavioral based, included education on psychology and physiology of pain, teaching of pain management strategies, analgesic treatment, socio-economic counseling, physiotherapy (MPT, n = 56), treatment by a general practitioner (GP, n = 58) vs. a group waiting 6	Baseline, 3, and 6 months.	At six months: MPT vs. WL-group, pain VAS (52±24 vs. 67±19, p ≤0.05), HAD (1.64 vs. 2.31, p ≤0.05), PGWB (62±17 vs. 51±20, p ≤0.05), SF-36-SFA (65±30 vs 57±32, p ≤0.05), SF-36-GH (44±23 vs. 32±20, p ≤0.05), no other significance in variables. MPT vs. GP, Pain VAS (52±24 vs. 65±25, p ≤0.05), PGWB (62±17 vs. 53±19, p ≤0.05), no other significance in variables.	"[I]n the MPT-group there was a significant reduction in pain intensity and improvement of HRQL [health related quality of life] compared to the WL-group, and the mere establishment of a pain diagnosis and a pain management play by a pain specialist was not sufficient to enable the referring GP to manage severely chronic pain patients."	No significance in WL group vs. GP.

						months before treatment initiated (WL-group, n = 53) follow-up 3 and 6 months.				

Evidence for Other Functional Restoration Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Smeets, 2005 (7.0)	Functional restoration	RCT	No mention of sponsorship. No COI.	N = 223 with chronic low back pain.	Mean age 41.43; 117 males, 106 females.	Active physical treatment, (APT) 5-minute warming up, 20 minutes performing at 65 to 80% of the maximum heart rate (HRmax) followed by a 5-minute cooling down. (N = 53) vs Cognitive-Behavioral treatment, (CBT) two introductory group meetings followed by 18 individual sessions. No physical exercise (N =58) vs Combined Treatment, CT consisted of APT in combination with PST 10 sessions	1 year	Outcomes compared to WL RDQ 13.88 vs APT -2.40, vs CBT -3.05, vs CT -2.56. Main complaints 74.25 vs APT -11.19, vs CBT -16.36, vs CT -17.84. APT & CBT vs CT RDQ 0.16, -0.49 vs 11.40 Main complaints, 6.65, 1.48 vs 54.68 Current pain -0.45, 1.48 vs 42.31.	"All three active treatments were effective in comparison to no treatment, but no clinically relevant differences between the combined and the single component treatments were found."	Waitlist control bias. Data suggest all 3 of the treatment arms showed improvement compared to control group but no one treatment group was superior to another.

						of 1 1/2 hours (CT) (N = 61) vs Waiting List (WL) (N = 51)				
Pires D 2015 (6.5)	Functional restoration	RCT	No COI. No sponsorship	N= 62 chronic low back pain patients	Mean age: 50.0 years 40 females, 22 males	Education group (n=20) vs Control group (n=32) Twelve sessions of a 6-week aquatic exercise programme preceded by 2 sessions of pain neurophysiology education. Controls received only 12 sessions of the 6-week aquatic exercise programme.	Post 6-weeks intervention, post 3-months follow-up	55 participants completed the study. Analysis using mixed-model ANOVA revealed a significant treatment condition interaction on pain intensity at the 3 months follow-up, favoring the education group (mean SD change: –25.4± 26.7 vs –6.6 ± 30.7, $P < 0.005$). Although participants in the education group were more likely to report perceived functional benefits from treatment at 3 months follow-up (RR=1.63, 95%CI: 1.01–2.63), no significant differences were found in functional disability and kinesiophobia between groups at any time.	"[T]his study indicates that the provision of pain neurophysiology education is a clinically effective addition to aquatic exercise. Further studies are necessary to better understand how pain neurophysiology education influences pain intensity and disability and to evaluate the long terms effects of this intervention on pain and disability."	Data suggest the combination group (aquatic exercise plus pain education) improved pain intensity but no other differences between groups.
Ris, 2016 (6.0)	Functional restoration	RCT	No COI. No sponsorship.	N= 200 traumatic/non-traumatic	Mean age: 45 years; 149	Pain education combined with exercises/	At baseline, after 4 months	The exercise group showed statistically significant improvement in	"A 4-month intervention containing pain education, specific	Data suggest combination physical training, specific

				neck pain patients	females, 51 males	training Exercise group (n=101) Vs. Pain education Control group (n=99)		physical HR-QoL, mental HRQoL, depression, cervical pressure pain threshold, cervical extension movement, muscle function, and oculomotion. Per protocol analyses confirmed these results with additional significant improvements in the exercise group compared with controls	exercises and graded activity training showed significant effect on improved HR-QoL, as well as on psychological factors, cervical extension, muscle function and some oculomotor functions. Good adherence increased the effect in favour of the exercise group. This may be an effective intervention for chronic neck pain patients	exercises and pain education is superior to pain education alone for improving QoL.
Archer, 2016 (score=6.0)	Functional restoration	RCT	Sponsorship by the national institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health.	N = 86 patients post lower lumbar surgery	Mean age 57.6; 38 males 48 females.	Education (N = 43) vs Cognitive-behavioral-based rehabilitation therapy(CBPT) weekly sessions with a study physical therapist for 6 weeks (N = 43)	3 months	CBPT vs Education post treatment .22 (p = .52) 3 months -.88 (p = .007) Leg pain Post treatment -.53 (p = .07) 3 mo -1.2 (p = .007)	"This randomized trial demonstrates that screening patients for fear of movement and using a targeted CBPT program results in significant and clinically meaningful improvement in pain, disability, general health, and physical performance after spine surgery for degenerative conditions"	Data suggest CBPT may improve chronic pain and other post-operative outcomes after spinal surgery as 3 month outcome follow-ups were statistically significant for pain improvement in CBPT groups.

Monrone, 2016 (score=5.5)	Functional restoration	RCT	Sponsored by national institutes of health no COI.	N = 282 patients with chronic lower back pain.	Mean age 74.5; 134 males and 148 females	Intervention 8 week mindfulness based stress reduction program. (N = 140) vs Control (N = 142)	6 months	Roland and Morris Disability Questionnaire; intervention group improved −1.1 points on the at 8 weeks and −0.4 points at 6 months (overall group × time interaction, P = .01). Mean overall change in pain scores. 30% improvement immediately after completion. Intervention group vs control group achieved a 30% improvement on the current (54 of 132 [40.9%] vs 34 of 138 [24.6%]; P = .004) and most severe (48 of 132 [36.4%] vs 30 of 138 [21.7%]; P = .008). 6 months (52 of 117 [44.4%] vs 34 of 135 [25.2%]; P = .001) and most severe (42 of 117 [35.9%] vs 30 of 135 [22.2%]; P = .02). Evaluation at 50% improvement at trial end. (21 of 132 [15.9%]vs 14of 138 [10.1%]; P = .16), current (43 of 132	"A mind-body program for chronic LBP improved short-term function and long-term current and most severe pain. The functional improvement was not sustained, suggesting that future development of the intervention could focus on durability."	Data suggest there were short term functional improvements from the mind-body group and pain improvement for severe and current long term pain in older adults. Medication u se not described.

								[32.6%]vs22of 138 [15.9%];P = .001), Most severe (21 of 132 [15.9%] vs 12 of 138 [8.7%]; P = .07) 6 months; (29 of 117 [24.8%] vs 18 of 135 [13.3%];P = .02) and current (41of 117 [35.0%]vs 28 of 135 [20.7%]; P = .01) not most severe (25 of 117 [21.4%] vs 17 of 135 [12.6%]; P = .06) NRS pain measures.		
Izquierdo, 2016 (5.5)	Functional restoration	RCT	No mention of Sponsorship or COI.	28 patients with chronic neck pain	Mean age 29.2; 10 males, 18 females.	(Cranio-cervical flexion test) CCF training (N = 14) Vs Proprioception training (N = 14)	2 months	NDI post month 2 CCF 4.46 vs Proprioception 4.14 Vas maximum median CCF.20 vs Proprioception 1.25 VAS minimum CCF 2.17 vs proprioception 2.05	"Training protocols of CCF and proprioception training produced an improvement in activation and endurance of the deep cervical flexors, as assessed via the CCFT, on pain measured by triple VAS and on the level of disability evaluated with NDI, with similar results in both groups. However, pressure pain sensitivity was not affected in either group. Proprioception training may provide an	Small sample. Data suggest comparable efficacy.

									additional benefit of facilitating the deep cervical flexor muscles."	
Bendix, 1996 (score=5.5)	Interdisciplinary work Rehabilitation program	RCT	Supported by grant from Danish Rheumatism Association, and Research Foundation of the Copenhagen University. No mention of COIs.	N = 106 with chronic LBP in Denmark	Median age: 41 for treated group, 40 for control group; 28 male, 66 females.	Multidisciplinary functional restoration (n = 55) vs. Control (n = 51). Multi-disciplinary program: aerobics, weight training, work stimulation/work hardening, relaxation, psychological group, stretching, theoretical class, recreation. Intervention full-time program with 135 hours for 6 weeks. Controls sent for treatment elsewhere.	4 months	Intervention group returned to work at much higher rate (64% vs. 29%). Median contacts with health care system were median 1.6 for treatment group vs. 5.3 for control, p <0.001. Sick leave days were median of 10 for treatment group vs. 122 for control, p = 0.02. Back pain ratings 5.7 for treatment group vs. 6.9 for control group, p = 0.05.	"Although such programs are expensive, they can reduce pension expenditures, sick leave days, health care contacts, and pain."	Large differences in contact time and untreated controls bias in favor of intervention. Program with many co-interventions and was intensive. Data suggest effective to reduce lost time in Denmark and applicability elsewhere uncertain.
Bendix, 1998 (score=5.5)	Functional Restoration	RCT	Sponsored by Danish Rheumatism Association, Danish Ministry of Health, National health Fund for Research and Development, Danish Society for Manual Medicine, Minister Erna Hamilton's	N = 185 participants with chronic low back pain.	Mean age: 42.2 years; 54 males, 131 females.	Two parallel groups: Group A1 (N = 46) functional restoration (FR, 8h/day X 3 weeks, then 6h/day X 3 weeks FR) and A2 control group (no treatment, N = 42) vs Group B1 FR (N = 37), B2 physical training	Follow-up at baseline and 5 years.	Comparing baseline to 5 year follow-up, statistically significant results were seen in being able to do more work in B1 (p=0.0006), decreased difficulties in ADLs due to LBP in both FR groups (p=0.001 for A1, p=0.0008 for B1), reduction in back pain for both A	"The overall result shows a positive long-term effect of the FR program, but it also shows the necessity of testing a given treatment in different projects and designs, among other things due to statistical variations."	Data suggest at 5 years the FR group showed a positive long term effect.

			Foundation, Foundation of Gerda and Aage Haensch, Research Foundation of Copenhagen University, Rockwool Foundation and more. No mention of COI.			only (N = 29), and B3 psychological support and physical training (N = 31, 2x/w for 6 weeks, total of 24 hours for B2 and B3).		groups (p=0.01 for both), decreased pain medication for back pain in group B1 (p=0.009), and increased sport activity for every group (p≤0.001). For increase in subjective quality of life, B1 was significantly higher compared to B2 (p=0.007) and B3 (p=0.003).		
Jessep 2009 (score=5.5)	Functional Restoration	RCT	Sponsored by Physiotherapy Research Foundation Project Number PRF/03/3. No COI.	N = 64 over age 50 with mild, moderate, or severe non-specific knee pain lasting more than 6 months, diagnosed with knee OA	Mean (range) age outptatient group 67 (51 to 76), ESCAPE group 66 (53 to 81). Females only.	Outpatient physiotherapy vs. ESCAPE-knee pain for knee osteoarthritis for maximum of 10 sessions.	Follow-up at baseline and 12 months.	Exercise beliefs and self-efficacy score, mean (SD): outpatient physiotherapy 68.2 (60) post intervention, 66.2 (6.9) 12 month follow-up compared to ESCAPE-knee pain 71.5(8.4) and 70.8 (8.2), p = 0.035.	"The hypothesis that ESCAPE-knee pain would sustain greater benefits than outpatient physiotherapy was not supported as both interventions produced similar sustained improvements in physical function and other clinical outcomes. Lower intervention costs and reduced healthcare utilisation did support the hypothesis that ESCAPE-knee pain would be less costly and more cost-effective than outpatient physiotherapy."	High dropouts. Multiple co-interventions. Data suggest comparable results at 1 year.

Hahne 2016 (score=5.5)	Functional Restoration	RCT	Supported by LifeCare Health. COI of authors Grant: LifeCare Health (Paid directly to institution/employer), pertaining to the submitted work; Consulting: LifeCare Health (D), outside the submitted work	N=54 with clinical features of radiculopathy (6-week to 6-month duration) and imaging showing a lumbar disc herniation.	Mean (SD) age advice group 46.9 (12.8), 44.5 (11.5) IFR group.	Individualized functional restoration incorporating advice (10 sessions) (N=28) vs. guideline-based advice alone (2 sessions) (N=26) over a 10-week period.	Follow-up 52 weeks.	Mean (SD) Activity limitation (Oswestry 0–100): Adjusted between-group difference (95% CI) was 8.2 (0.7–15.6), p=0.03.	"[I]ndividualized functional restoration incorporating advice was more effective than guideline-based advice alone for achieving faster improvement in back pain (10-week follow-up) and faster (10 weeks) and sustained (52 weeks) improvement in activity limitation, but not for improvement in leg pain"	Medication use missing in baseline comparison table. Data suggest individualized functional restoration experienced greater improved back pain and activity vs advice group at 52 weeks.
Masharawi 2013 (score=5.0)	Functional Restoration	RCT	No mention of sponsorship or COIs.	N=40 with non specific chronic low back pain (NSCLBP).	Mean age exercise group 52.45 (10.6), control group 53.6 (9.53). Females only.	NWB bi-weekly group exercise class aimed at improving lumbar mobility/flexibility and stability (N=20) vs. control group (N=20).	Follow-up at 4 weeks of intervention and 8 weeks later.	VAS score significantly reduced following intervention and at follow up vs. control group (mean difference = 2.32 (−58%), $p < 0.001$.	"A functional program of NWB group exercising improves functional, painful status, lumbar flexion and extension ranges of motion in women suffering from NSCLBP."	Waitlist control bias. Data suggest NWB group had better pain relief vs controls.
Hurley 2015 (score=5.0)	Functional Restoration	RCT	The Health Research Board Project Grant 2007/79 funded this research. No COI.	N=246 with chronic low back pain.	Mean age±SD: 45.4±11.4 years. 79 males, 167 females.	Individualized walking program (WP) (N=82) vs. group exercise class (EC) (N=83) vs. usual physiotherapy (UP, control) (N=81)	Follow-up 12 months.	Mean Oswestry Disability Index (0-100): Baseline vs. 12 months EC Group 33.52 vs. 26.93. WP Group 33.52 vs. 26.67.	"Supervised walking provides an effective alternative to current forms of CLBP management."	Usual care bias. Data suggest equal outcomes in all 3 groups but the WP group had largest adherence.

Rudolfsson T 2014 (4.5)	Functional restoration	RCT	Sponsored by Alfta Research Foundation, grants from the Swedish Council for Working Life and Social Research (2006-1162) and Länsförsäkringar Forskning och Framtid (51-1010/06). No mention of COI.	N= 128 women with chronic non-specific neck pain	Mean age: 51.2 years; all females	Neck coordination exercise NCE with novel training device (n=36) Vs. Strength Training ST for the neck and shoulders (n=36) Vs. Massage (n=36)	Six month follow up	No significant treatment effects in favor of neck coordination exercise were found for short-term or 6-month evaluations.	"Neck coordination exercise is no better than strength training and massage in improving sensorimotor function. Further research should investigate the use of cutoffs for sensorimotor dysfunctions prior to proprioceptive or coordinative training.	Data suggest comparable in efficacy between groups.
Roche-Leboucher, 2011 (score=4.0)	Chronic Pain Management Programs/Functional Restoration Programs	RCT	Sponsored by Institut National de veille sanitaire, Paris, France. No COI.	N=132 patients with low back pain	Mean age: 39.8 years; 86 males, 46 females.	Functional Restoration Program (n=68) – Patients performed muscle strengthening, endurance training, balneotherapy, and attended psychologist meetings. Vs. Active Individual Therapy (n= 64) – Patients focused on flexibility training and pain management.	1 year.	The reduction in number of sick-leave days (posttreatment year – pretreatment year) for functional restoration is 64 ($p<0.001$) and for Active Individual Therapy is 49 ($p<0.001$).	"Both programs are efficient in reducing disability and sick-leave days. The FRP is significantly more effective in reducing sick-leave days. Further analysis is required to determine if this overweighs the difference in costs of both programs."	Data suggest FRP effective with less sick leave, increased fitness, and trends towards greater return to work and full time work (the latter 2 are underpowered).

Bendix, 2000 (score=4.0)	Functional Restoration	RCT	Sponsored by Danish Rheumatism Association, Gerda and Aage Hensch Foundation, Director Ib Henriksen's Fund, Insurance Company for Industrial Injuries, Lilly Benthine Lunds Fund, DANICA Pension, Municipal Pension Insurance Company Ltd., and Danish Society for Manual Medicine. COI, category 14.	N = 99 participants with chronic low back pain.	Mean age: 42 years; 31 males, 68 females.	Functional Restoration Program (FR, N = 48) for 39 hrs/week for 3 weeks, vs Outpatient Intensive Physical Training (OIT, N = 51) for 1.5 hrs 3x/week for 8 weeks.	Follow-up at baseline and 1 year.	The only statistically significant difference between groups at the one year follow-up favored FR (p=0.03) in the overall assessment (subjective improvement of quality of life on a 5-point scale).	"Functional restoration (FR) was superior to an outpatient intensive training program in overall assessment, whereas all other tested clinical or work-related variables did not differ between the two programs."	Data suggest FR better than outpatient PT program but only in overall assessment and more costly. Medication use not described.
Engbert 2011 (score=4.0)	Functional Restoration	RCT	No funds were received in support of this work. No COI reported.	N = 23 patients with chronic low back pain.	Mean age 48.7 (SD=9.7) years). 11 males, 12 females.	Therapeutic Climbing (TC) group received 4 weeks of training 4 times a week on an indoor training wall (4 m x 2.5 m) (n = 14) vs. Standard exercise regime (SRE) group also received 4 training sessions	Follow-ups were at baseline and after 4 weeks of treatment.	After 4 weeks of training, there was a significant difference in SF-36: Physical Health subscales of physical functioning (TC: 86.50 ± 15.1 vs. SRE: 75.50 ± 16.7, p = 0.01) and general health (TC: 71.10 ± 13.6 vs. SRE: 62.85 ± 12.4, p = 0.01).	"This study demonstrates that therapeutic climbing may be suitable for patients with chronic low back pain. The therapeutic climbing regime especially improved the perceived health and physical functioning of patients, possibly through changes in attentional focus	Small sample size. Methodological details sparse.

						a week for 4 weeks (n = 14).			and new learning experiences regarding movement and pain."	
Frih 2009 (score=4.0)	Functional Restoration	RCT	No mention of sponsorship or COIs.	N = 107 with chronic low back pain or CLBP, eighty-two women.	Mean age 35.7. 82 females, 25 males.	Group A or home-based rehabilitation program received 4 sessions, 2-hours each with a total of 18 exercises (N = 54) vs. Group B or a standard rehabilitation program with 90 minutes of treatment a day, three times a week (N = 53).	Follow-up at baseline and four weeks and three, six and 12 months later.	Between time0 and time4 time points: pain intensity / FTF distance / and TL angle: in Gr A, -25.1, $p < 0.001$ and Gr B -13.9, $p < 0.001$ / 7.3 cm compared to 5 cm, $p < 0.001$ / and, 8.4º compared to 9.9º in group B, $p < 0.001$. Pain intensity between months 3 and 6, $p < 0.05$ and 6 and 12, $p = 0.199$. Quebec functional index between 6 months and one year, for Gr A -0.5 and Gr B 3.9, $p = 0.018$.	"[A] home-based rehabilitation program is as effective as standard physical therapy."	Multiple outcomes measured at timepoints. Comparable efficacy between programs.
Jeitler 2015 (score=4.0)	Functional Restoration	RCT	Supported by grants from the Else Kroner-Fresenius-Stiftung and the Karl and Veronica Carstens Stiftung, Germany. No COI.	N=89 with chronic neck pain.	Mean age 49.7±10.5 years. 73 females, 16 males.	8-week meditation program (jyoti meditation) with weekly 90-minute classes (n=45) vs. home-based exercise program (n=44).	Follow-up 8 weeks.	Reduction of 45.5±23.3 mm to 21.6±17.2 mm in the meditation Group vs. 43.8±22.0 mm to 37.7±21.5 mm in the exercise group; mean difference: 13.2 mm; p=0.02.	"[M]editation may support chronic pain patients in pain reduction and pain coping. Further well-designed studies including more active control comparisons and longer-term followup are warranted."	Waitlist control bias. Data suggest meditation reduced pain at rest but not disability in neck pain patients.

Bearne 2011 (score=4.0)	Functional Restoration	RCT	Funded by the Physiotherapy Research Foundation, administered by the Chartered Society of Physiotherapy. M.H. and N.W. are funded by the Arthritis Research UK.	N=48 with chronic hip pain.	Mean (range) age usual care: 67 (53-78), rehabilitation 65 (52-76). 34 females, 14 males.	Five week exercise and self-management program (N= vs. continue under the management of their general practitioner (GP).	Follow-up at baseline, post-intervention (or after six weeks) and six months post-intervention.	No differences between the groups (all p > 0.05).	"The moderate effects in all outcomes immediately following rehabilitation suggested that it warrants further investigation. Issues with diagnosis and adaptations to the programme were identified and will be addressed in a randomized controlled trial."	Usual care control bias. Data suggest moderate improvement in rehabilitation group. Attrition rate (25%) comprised of worst functioning in treatment group and best functioning in control group may have under or overestimated effect.

Evidence for Participatory Ergonomic Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Lambeek, 2010 (score=7.5)	Participatory Ergonomic s Program	RCT	No sponsorship or COI.	N = 134 with LBP >12 weeks, paid for work for at least 8 hours/week, and absent or partially absent from work.	Mean age of Integrated care group: 45.5, Usual Care group: 46.8. Sex(M:F) 78:56	(UC)Usual Care (n = 68) vs. (IC) Integrated Care (n = 66) (coordinated by OM physician, including participatory ergonomics, graded activity program with CBT principles)	Follow-ups after 3, 6, 9, and 12 months.	No differences for pain improvements. Mean pain improvement; (3-months IC= 1.11, UC = 1.59(n = 123)), (6-months IC = 1.26, UC= 2.26(n = 123)), (12-months IC = 1.64, UC = 1.85(n = 121)). Difference between groups with (95% CI); 3-months 0.99 (-1.3 to 2.1), 6-months 0.49 (-0.6 to 1.6), 12-	"The integrated care programme substantially reduced disability due to chronic low back pain in private and working life."	Usual care comparison may bias in favor of intervention. However, marked differences suggest efficacy.

								months 0.21 (-0.8 to 1.2). 3-months p = 0.08, 6-months p = 0.37, 12-months p = 0.67		
Lambeek, 2010 (score=7.5)	Participatory ergonomics program	RCT	No sponsorship or COI.	N = 134 with LBP >12 weeks, paid for work for at least 8 hours/week, and absent or partially absent from work.	Mean age of Integrated care group: 45.5, Usual Care group: 46.8. Sex(M:F) 78:56	(UC)Usual Care (n = 68) vs. (IC) Integrated Care (n = 66) (coordinated by OM physician, including participatory ergonomics, graded activity program with CBT principles)	Follow-ups after 3, 6, 9, and 12 months.	Cost-benefit shows that for every £1 going towards IC, £26 estimated to be returned to company. Mean (SD) for total effects; (days to RTW: IC = 129 (117), UC = 197 (129), (QALY) quality adjusted life years: IC = 0.74 (0.19), UC = 0.65 (0.21)) and Mean difference (95% CI) -68 (-110 to -26) for RTW, and 0.09 (0.01 to 0.16) for QALY. Mean (SD) for total Costs; (Primary care costs: IC = 1251 (700), UC = 857 (758)), (Total indirect costs: IC = 11686 (12553), UC = 17213 (13416)), and (Total cost: IC = 13165 (13600), UC = 18475 (13616)). Mean difference (95% CI); (Primary care costs: 395 (131	"Implementation of an integrated care programme for patients to significantly reduce societal cost, increase effectiveness of care, improve quality of life, and improve function on a broad scale. Integrated care therefore has large gains for patients and society as well as for employers."	Precision of economic analyses outside UK questionable, however, large magnitude of differences in favor of the intervention.

								to 687), (Total indirect costs: -5527 (-10160 to -740), and (Total cost: -5310 (-10042 to -391).		
Steenstra, 2003 (score=5.5)	Participatory Ergonomics Program	RCT	No mention of sponsorship. No COI.	N = 196 workers on sick leave 2-6 weeks because of LBP.	Mean age of Workers on sick leave with workplace intervention (WI): 44.0, On sick leave without WI: 41.2. WI with Clinical Intervention (CI): 43.6. WI without CI: 43.5. Usual care (UC) with CI: 39.2, UC without CI: 43.3. Sex(M:F) 84:112	Workplace intervention (WI, n = 96) vs. usual care (UC, n = 100). WI Randomization: WI+CI (n = 27) vs. WI (n = 25). UC randomization: UC+CI (n = 28). WI: UC, workplace assessment plus work modification, RTW counselling. CI (2x a week): operant behavioral therapy principles, physical exams, functional capacity evaluations. UC followed Dutch guidelines. Final follow-up at 52 weeks.	12, 26, 52 weeks	Clinical intervention vs. usual care lasting return to work mean improvement±SD for workplace intervention first 8 weeks, usual care first 8 weeks: 160.78± 78.66/109.88±62.55, 172.75± 85.87/151.41±105.11. Functional status: -8.29±6.98/-10.08± 5.77, -6.12±4.62/-9.18± 6.87. Pain severity: -2.41± 2.39/-2.79±2.98, -2.07± 2.32/-3.06±3.15. Quality of life: 0.22± 0.25/0.27±0.30, 0.19±0.21/0.30±0.31. General health: 11.77±21.42/160.78± 78.66, 6.04±21.44/14.48±22.71.	"The workplace intervention results in a safe and faster RTW than usual care at reasonable costs for workers on sick-leave for two to six weeks due to LBP."	Earlier RTW shown. Applicability to U.S. unclear, especially as Dutch guidelines recommends resuming usual activities and work on relatively slow basis of within 2 weeks.
Anema, 2007 (score=5.5)	Participatory Ergonomics Program	RCT	Supported by the Netherlands Organization for Health Research and Development	N = 196 sick listed 2-6 weeks due to non-specific LBP.	Mean age of workers on Sick leave > weeks with	Workplace intervention: worksite assessments and work	52 weeks	Time to full and lasting return to work in graded activity group 144 days vs. 111 days in	"Workplace intervention is advised for multidisciplinary rehabilitation of subacute LBP. Graded	Workplace intervention removed approximately 43% of

			(ZonMw), Dutch Ministries of Health, Welfare and Sports and of Social Affairs. Federal funds received in support of this work. No industry sponsorship or COI.		workplace interventio n (WI): 44.0, without WI: 41.2. Workers on sick leave > 8 weeks with graded activity (GA): 41.3, without GA: 43.4. Sex(M:F) Workers on sick leave > 2 weeks (84:112), Workers on sick leave > 8 weeks (45:67)	adjustments (n = 96) vs. Usual care: Dutch occupational guidelines for LBP, education, coping with LBP (n = 100) for 8 weeks, followed by 2nd randomized trial of graded exercise for those not returning to work (n = 112) start of therapy median 69 days after lost time began. Follow-up to 1 year.		usual care group, p = 0.030. Total number of sick leave days during 12 month follow-up for graded activity 145 vs. 111 for usual care group, p <0.001.	activity or combined intervention is not advised."	patients before 2nd randomizati on. Time to onset of exercise >2 months after lost time began, compliance poor (65%), and exercise program structure appears variable based on wide range in number of sessions indicating robust conclusions on graded exercise components not warranted. Applicability outside Netherlands unclear.
Hagen, 2000 (score=4.5)	Participatory Ergonomics Program	RCT	Sponsored by the Norwegian Ministry of Health and Social Affairs. No industry sponsorship or COI.	N = 510 with subacute LBP and 8 to 12 weeks lost time in Norway	Mean age: 40.9±10. Sex(M:F) (238:219)	Light mobilization program plus education regarding fear of back pain (n = 254) vs. Usual care treated by primary health care provider (n = 256).	3, 6, 12 and 24 months.	RTW at 3 months favored program (51.9% vs. 35.9%, RR = 1.45, 95% CI 1.17 to 1.79). Differences persisted at 6 months (61.2% vs. 45%, RR=1.36, 95% CI 1.14 to 1.62) and 12 months (68.4% vs. 56.4%, RR = 1.21,	"…[P]atients with subacute LBP return to work sooner if they are referred to a spine clinic offering consultation with examination, information, reassurance, and encouragement to engage in physical	Data suggest early intervention by provider and fear avoidance activities improve outcomes in LBP. Whether

								95% CI 1.05 to 1.40), though narrowed modestly. Intervention group with fewer days of sickness compensation (mean 95.5 vs. 133.7 days, p = 0.0002).	activity as normally as possible. It cannot be determined from the data whether all the components of the intervention are necessary, but we believe that the whole integrated "package" is important."	this requires a spine clinic is not tested and appears dubious.
Loisel, 1997 (score=4.0)	Participatory Ergonomics Program	RCT	Grant from Institute de la Recherche en Sante et Securite du Travail du Quebec (IRSST), Canada. No industry sponsorship or COI.	N = 130 with back pain	Mean age of Usual care group: 41.7, Clinical group: 40.2, Occupational group: 44.8, Full group: 43.8. Sex(M:F) 62:42	Usual care (n = 26) vs. clinical intervention: after 8 weeks absence visit to "back pain specialist," back school; after 12 weeks absence, multi-disciplinary work rehab intervention (n = 31) vs. occupational intervention: after 6 weeks absence visit to OT, ergonomics evaluation (n = 22) vs. full intervention (combined last two) (n = 25).	Follow-up at 12, 24, and 52 weeks.	RTW rate 2.23 times greater in occupational intervention group vs. usual care, p = 0.04. Median duration of work absence was 60 days for full intervention, 67 for occupational intervention, 131 for clinical intervention, and 120.5 days for usual care group, p = 0.01 for occupational effect groups vs. the 2 groups without intervention.	"Close association of occupational intervention with clinical care is of primary importance in impeding progression toward chronicity of low back pain."	Involved disciplines were occupational physicians, ergonomists, "back specialists," and apparently physiotherapists. Long times off work atypical for U.S. and unclear if results generalizable outside the Netherlands.
Jousset, 2004 (score=4.0)	Participatory Ergonomics Program	RCT	Supported by Union Regionale des Caisses d'Assurance Maladie des Pays de Loire. No industry sponsorship or COI.	N = 86 chronic LBP, nonlimited work contract, "threatened" job by CLBP, no relieve by medical or	Mean age of functional restoration group: 41.4, Active individual therapy	Functional Restoration Group vs Active Individual Therapy Group Functional restoration group (n = 44) vs. Active	6 months	No difference in pain intensity between 2 groups. After 6 months, Functional restoration had mean of 3.1 and SD of 2.5, while Active individual therapy	"[T]he effectiveness of a functional restoration program on important outcome measures, such as sick leave, in a country that has a social system that protects	More surgeries in FR group (35 v 15%). Trend to less sick leave and several other measures

				surgery intervention.	group: 39.4. Sex(M:F) 56:28	individual therapy group (n = 42).		had mean of 4.0 & SD of 2.8. (p = 0.16)	people facing difficulties at work."	positive in favor of FR. Data suggest efficacy of FR in France.
Driessen, 2011 (score=4.0)	Participatory Ergonomics Program	RCT	Cluster RCT Grant from Netherlands Organization for Health Research and Development (ZonMw). No industry sponsorship or COI	N = 3047 with LBP and or neck pain (NP); no cumulative of sick leave >4 weeks due to LBP or NP 3 months prior	Mean age of Interventio n group: 41.9, Control group: 42.1. Sex(M:F) 1,785:116	Intervention group comprised of PE and ergonomic measures (n = 1472 workers) vs. Control group without PE measures (n = 1575 workers).	12 months	Intervention effects during 12 month follow up period: From no symptoms to symptoms for LBP: OR = 1.23, 95% CI, 0.97-1.57, p = 0.08. From symptoms to no symptoms for LBP: OR = 1.41, 95% CI 1.01-1.96, p = 0.04. Intervention effects for LBP: OR = 0.73 after 3 months, OR = 0.87 after 6 months, OR = 1.11 after 9 months, OR = 1.16 after 12 months, p >0.05.	"PE neither reduced low-back and neck pain prevalence nor pain intensity and duration nor was it effective in the prevention of low-back and neck pain or the recovery from neck pain."	Pooling of 3 studies. Cluster randomized by dept. Some baseline differences. High dropouts. Unclear if results from Netherlands applicable elsewhere. Data suggest largely ineffective.
Lambeek, 2007 (score=4.0)	Participatory ergonomics program	RCT	Granted by: VU University Medical Center, TNO Work & Employment, Dutch Health Insurance Executive Council (CVZ), Stichting Instituut GAK (SIG) and The Netherlands Organisation for Health Research and Development (ZONMw). No industry sponsorship or COI.	N = 130 with LBP >12 weeks, paid work for at least 8 hours/ week, and on partial sick leave age 18-65	No gender or age distribution described.	Usual clinical medical care (n = 65) vs. Workplace intervention (n = 65)	3, 6, 9, and 12 months	Significant reduction in sick leave through workplace intervention. Results indicated 29-105 days reduced for sick leave.	"Usual care of primary and outpatient health services isn't directly aimed at RTW, therefor it is desirable to look for care which is aimed at RTW. Research shows that several occupational interventions in primary care are aimed at RTW. They have shown a significant reduction of sick leave for employee with LBP."	Only a study protocol.

Barriers to Optimizing the Management of Pain

Summary of Recommendations

The following summary table contains recommendations for evaluating and managing behavorial interventions from the Evidence-based Chronic Pain Panel. These recommendations are based on critically appraised higher quality research evidence or, when such evidence was unavailable or inconsistent, on expert consensus as required in ACOEM's Methodology. Recommendations are made under the following categories:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient – Recommended (Consensus-based), "I" Level
- Insufficient – No Recommendation (Consensus-based), "I" Level
- Insufficient – Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

Psychological Evaluation for Chronic Pain Patients	**Recommended, Insufficient Evidence (I)**
Cognitive Behavioral Therapy for Patients with Chronic Pain	**Moderately Recommended, Evidence (B)**
Fear Avoidance Belief Training	**Recommended, Insufficient Evidence (I)**
Biofeedback	**Recommended, Insufficient Evidence (I)**

Overview

Pain is a psychological phenomenon that is influenced by a myriad of biomedical and psychosocial factors. An approach to pain assessment that has shown considerable promise has been the assessment of cognitions related to pain, particularly the assessment of pain catastrophizing and fear avoidance (i.e. kinesiophobia) (Roelofs 04). This approach naturally leads to behavioral interventions.

The traditional approach to assessing and treating pain uses an ordinal pain scale (0 to 10). Unfortunately, a patient's pain report may be confounded by a variety of variables including: 1) the perception of pain, and especially chronic pain has a low correlation with pathophysiology, 2) the perception of pain is influenced by psychological variables such as mood, arousal, attention and cognition, and 3) the patient may be incentivized to alter reports of pain. Thus, there is increasing use of function-centered questionnaires to determine the degree to which pain impacts function, although these too are usually subjective. Advancing research using fMRI and similar technologies may develop into objective method(s) of identifying brain activity that corresponds and corroborates pain complaints [1396-1399]. However, these imaging techniques require further study in workers, as they may produce problematic findings (e.g. the patient's brain image suggests pain activity, although the patient does not

report pain). These challenges present further problems as psychological and behavioral issues that impact pain and function may go unaddressed while being of critical importance.

When patients are assessed psychologically, pain problems are generally evaluated with various psychological instruments that provide qualitative and quantitative inferences about the patient's perceptions and related behaviors. Addressing pain-related dysfunction, psychological comorbidities (e.g., anxiety, fear, depression, anger, hopelessness, stress) and engaging in problem solving to address social roadblocks to recovery is usually more helpful than focusing on analgesia. One treatment approach with considerable evidence of success is cognitive behavioral therapy (CBT). CBT recognizes the pain, but works to change the patient's negative thoughts about the pain and its impacts, including the development of constructive skills, coping and behaviors related to the pain.

The way in which the provider manages the patient with delayed recovery may affect the degree to which chronic pain behaviors develop. As pain is a biopsychosocial phenomenon, a formal psychological evaluation (which may include appropriate diagnostic psychological testing) may be helpful (see below). In addition to identifying psychological risk factors, the identification of any social risk factors is also important (See Cornerstones of Disability Prevention and Management Guideline). Social risk factors may include work-related issues such as job satisfaction or co-worker support, family reinforcement of pain behaviors or lack of support, and legal/financial incentives for poor recovery. Additionally, cultural beliefs regarding origins of disease and health care patterns may also influence presentation and recovery. These should be addressed in a positive, cooperative and sensitive manner to facilitate recovery and minimize the chance of physical debilitation and chronic or long-term disability. [113]

Treating chronic pain syndromes requires specialized knowledge, substantial time, and access to multiple disciplines if not multidisciplinary care. Judicious involvement of other health care professionals (e.g., psychologists, occupational and physical therapists, etc.) who can offer diagnostic assessments and additional therapies where indicated, while the provider continues to direct the therapeutic process to maximize functional restoration. Close communication between all treating professionals is essential.

Psychological Services

Psychological and behavioral factors are key components of subacute and chronic pain conditions as: (i) risks of development of chronic pain (e.g., pre-existing anxiety [67, 82, 1400-1402], depression [67, 1401, 1402], catastrophizing, somatization [67], fear avoidant beliefs ("kinesiophobia") [100] (Malfliet 16;), fear of reinjury [100], job dissatisfaction, job instability, inadequate coping skills, familial social support, workplace social support; alcoholism [1401]; and (ii) risks from chronic pain (e.g., development of, or recurrence of anxiety [84, 1402], depression [1401-1403], catastrophizing, job instability, social estrangement, familial instability). (These issues are described in the Chronic Pain Guideline's Introduction and Basic Principles.) Psychological evaluation and treatment should be strongly considered for patients with chronic pain. Since such patients often present difficulties in diagnosis, rehabilitation, appropriateness for invasive procedures, and return to work planning, consultation can be helpful in these areas. Additionally, through behavioral medicine even those with relatively low levels of formal psychopathology may learn better ways of self-managing symptoms and therefore optimize their pain outcomes. As well, those with subacute pain who are not improving as expected are also candidates for psychological evaluation to improve function and to develop a plan to avoid chronic pain behaviors.

Psychological Evaluation for Chronic Pain Patients

Recommended.

A psychological evaluation is recommended as part of the evaluation and management of patients with chronic pain in order to identify psychosocial barriers that are contributing to disability and inhibiting function and to assess whether psychological factors will need to be considered and treated as part of the overall treatment plan.

Strength of Evidence – **Recommended, Insufficient Evidence (I)**
Level of Confidence – **Moderate**

Indications: Moderate to severe chronic pain patients who have:

1. Cases in which significant psychosocial dysfunction is observed or suspected.
2. The provider has need to understand psychosocial factors contributing to the patient's pain reports and disability behaviors
3. *Inadequate recovery:* This includes continued dysfunctional status despite a duration which exceeds the typical course of recovery; failure to benefit from indicated therapies or to return to work when medically indicated; or a persistent pain problem which is inadequately explained by the patient's physical findings.
4. *Medication issues and/or drug problems:* This includes any suspicion of drug overuse or misuse, aberrant drug behavior, substance abuse, addiction, or use of illicit substance, or for consideration of chronic use of opioids. [44, 590, 877, 878]
5. Current or premorbid history of major psychiatric symptoms or disorder.
6. *Problems with compliance/adherence with prescribed medical treatment or rehabilitation program:* For evaluation of candidly for or potential benefit from a proposed functional restoration program, e.g., comprehensive occupational rehabilitation or interdisciplinary pain rehabilitation (see Functional Restoration).
7. *Evidence of possible cognitive impairment which is associated with related significant ADL dysfunction:* This may be secondary to injury and/or possible adverse effects of medical therapies initiated for the chronic pain.
8. Catastrophic injuries with significant pain related or other dysfunction, e.g., spinal cord injury. [879-881]
9. Cases for which certain procedures are contemplated, e.g., back surgery (see Low Back Disorders Guideline) or spinal cord stimulation.

Benefits: Identify psychological factors that may maintain chronic pain and disability, begin treating and remove barriers to rehabilitation, and facilitate recovery and restoration of function.

Harms: Negligible. The implications of requesting a psychological evaluation are often misconstrued to imply that the purpose is an accusation. Though such diagnoses may be rendered, this does not necessarily imply a "psychological" or "mental" cause for the symptoms and signs.

Frequency/Dose/Duration: One comprehensive psychological evaluation should be performed by an independently licensed psychologist. Ongoing treatment as indicated by the results of the initial evaluation. Content follows. [882-885]

1. *Appropriate review of records:* The referring provider should assist in providing medical record documentation. Other information is sometimes reviewed, as necessary, e.g., from a family assessment, job description, etc.

2. *Clinical interview with patient:* The following parameters should be described from this interaction and other data obtained: History (including mental health, physical health, work, educational, legal, and substance use history), description of the pain, disability and/or other clinical problem, analysis of medication usage, social history, mental status, and behavioral assessment (including, as necessary, ADL, functional issues, and operant parameters, e.g., pain/illness behavior and environmental influences).

3. *Psychological testing:* A battery of appropriate diagnostic psychological tests should be administered and interpreted, as necessary. This should include instruments with evidence of validity and/or appropriate normative data for the condition or problems being assessed and have known value in differential diagnosis or treatment planning.(886) In selecting test instruments, the clinician should consider: 1) the appropriateness of the test(s) for the patient's presenting complaints and condition; 2) the appropriateness of a test(s) given the degree to which the patient's medical, gender, race/ethnicity, age, educational and other group status was represented during the test(s) development; 3) how a patient's performance in comparison to normative data will be useful in diagnosis or treatment planning; 4) the prognostic value of interpreted test data for certain treatments; and/or 5) whether the sensitivity and specificity will enhance the accuracy of a diagnosis (more specific test information is found in Appendix 1). Indications for psychological tests may include circumstances when:

   a. understanding factors contributing to the patient's pain reports and disability behaviors;

   b. a mental disorder is suspected;

   c. evaluating for a functional restoration program;

   d. the evaluation is part of a pre-surgical assessment;

   e. there is suspicion of cognitive impairment;

   f. the veracity of the complaint is at issue.

   Standardized psychological testing should be done as a part of a comprehensive mental health evaluation, as properly performed psychological testing enhances the reliability and value of a psychological evaluation. Psychological testing is usually performed by a psychologist, but psychiatrists or other physicians also perform such assessments if it is within the scope of their training and experience. [887, 888] Standards for the psychological assessment of patients with chronic pain have been reviewed elsewhere [1404]. Additionally, both

evidence and expert consensus regarding what variables should be assessed in these evaluations has also been reviewed [63]. The test battery for evaluation of patients with chronic nonmalignant pain includes, but is not limited to:

a. test(s) for assessment of the presenting pain, and/or other related health complaints or dysfunction;

b. test(s) of personality and psychopathology;

c. brief cognitive testing, when there is suspicion of CNS impairment;

d. *diagnostic impressions:* These should be inferred according to the ICD-10 [157]

e. *summary:* The psychological evaluation should provide both cogent explanations for the identified complaints and dysfunction, and recommendations for management. (see Appendix 1 for examples of tests)

Indications for Discontinuation: Largely negative results from an evaluation, resolution, and/or treatment to a level of acceptable stability.

Rationale: There are no quality trials of psychological evaluations, although there are many trials of specific interventions. Such assessments are routinely accomplished for the various purposes given above, including treatments for which various levels of evidence are provided herein, e.g., functional rehabilitation or interdisciplinary pain programs, candidacy for certain procedures, or chronic use of opioid medications.

Chronic pain problems are usually maintained by a variety of medical, physical, social, psychological, and occupational factors; the general purpose of a psychological evaluation regarding chronic pain is to comprehensively evaluate these influences. However, most pain complaints and functional deficits arising from musculoskeletal injuries resolve spontaneously or respond adequately to initial conservative treatment. Psychological evaluation should be considered for patients with chronic pain, i.e., where the pain problem or dysfunction persists longer than typical for the associated condition. Notwithstanding the numerous risk factors for development of chronic nonmalignant pain, the prediction of chronicity based on psychological evaluation of a specific patient has not been reliably demonstrated. The general purpose of the psychological evaluation is to: 1) describe and diagnose the current psychological and psychosocial dysfunctions; 2) describe psychological strengths; 3) elucidate the current psychological and behavioral factors which are salient in maintaining the complaints and dysfunction; 4) assess the likely premorbid factors which may be contributory; and 5) recommend treatment, management, and/or occupational/vocational options.

Psychological testing conducted outside the context of a qualified mental health evaluation has not been evaluated in quality studies and is believed to either provide little if any helpful information for the treating provider, may be potentially misleading, and psychological test results outside settings comparable to those used for standardization may be uninterpretable. Tests used in isolation

provide questionable clinically useful diagnoses or prognostic information for various procedures (see below).

The professional consensus is that the use of automated or computerized interpretation of standardized psychological instruments without adequate clinical correlation is inappropriate, although there are no large quality studies to evaluate that potential approach. Interpretation is best accomplished in the context of the individual patient mental health examination with corroboration of other clinical findings. [889, 890] Ethically, it is always preferable to conduct psychological evaluation and standardized testing in a patient's preferred language and in consideration of unique cultural issues. [887-889] Where alternate language forms of specific psychological test instruments are utilized, there should be assurance of appropriate validity. Assessments performed via a translator should be avoided whenever possible. When done in this fashion, errors, distortions, and misevaluation of patients' mental status and other parameters may occur. [891-894] When performed in this manner, the increased potential for a distorted assessment of the patient should be taken into consideration and documented.

Psychological evaluations are not invasive, have negligible adverse effects, are moderate cost, have clinical evidence of efficacy and are thus selectively recommended.

Evidence: There are no quality studies evaluating psychological evaluation for treatment of chronic nonmalignant pain or chronic pain syndromes.

Psychological Treatment/Behavioral Therapy

Psychological or behavioral treatments are commonly provided to patients with chronic pain syndromes. Patients who should be more strongly considered for these services include those with one or more of the following: delayed recovery, ineffective pain coping skills, psychological disorder(s), insomnia, stress-related psychophysiological responses such as muscular bracing, problematic medication use, excessive fear avoidant beliefs, and/or non-adherence with prior physical activity or other prescriptions. Where indicated, this has been typically provided with cognitive-behavior therapy (CBT). This is a type of psychotherapy which emphasizes the relationship of cognitions, behaviors, and mood to physical symptoms in an attempt to promote specific therapeutic goals. CBT techniques generally employ "homework" assignments in addition to direct psychotherapeutic treatment, and because of that CBT protocols have varying requirements for literacy. The provision of therapy does not generally require an ICD-10 diagnosis, though this is often obtained in patients with chronic pain syndromes, and many such patients *may* meet criteria for various diagnoses. Other diagnoses frequently include insomnia, post traumatic stress disorder, somatoform disorders, depression and/or anxiety disorders. Note that CBT treatments for chronic pain, depression, insomnia etc. are distinct therapies with unique protocols.

Cognitive Behavioral Therapy for Patients with Chronic Pain

Recommended.

Cognitive-behavioral therapy is moderately recommended for treatment of subacute and chronic pain.

Strength of Evidence – **Moderately Recommended, Evidence (B)**
Level of Confidence – **High**

Indications:	Indications for the use of CBT in chronic pain conditions include: 1. Inadequate results from traditional physical therapy and exercise program; 2. clinically significant problems of noncompliance or non-adherence to prescribed medical or physical regimens; 3. Mood disorders that complicate the management of the pain condition 4. vocational counseling for resolution of psychosocial barriers in return to work (requires a current or imminent medical release to return to work); 5. resolution of interpersonal, behavioral, or occupational self-management problems in the workplace, during/after return to work, where such problems are risk factors for loss of work or are impeding resumption of full duty or work consistent with permanent restrictions; and 6. Management of clinically significant behavioral aberrations and/or anxiety during opiate weaning or detoxification. 7. Sleep disturbance due to pain (Currie 00)
Benefits:	Improvements in management of pain, functioning in home, work and community settings. Reduced disability (Linton 05). May improve success of return to work process. May ease opioid weaning process. Reported volumetric increases measured by MRI in brain regions associated with pain control that were correlated with reductions in pain catastrophizing. (Seminowicz 2013)
Harms:	Negligible.
Frequency/Dose/Duration:	CBT psychotherapy provided either independently (Lamb 2010) or as a component therapy integrated into a program that includes physical therapy, such as an interdisciplinary or other functional restoration program (Monticone 2013), especially where the primary complaint is LBP. Established protocols for CBT require from 16 hours (Lamb, 2010; Monticone, 2013) to up to 24 hours to accomplish (Gyani, 2013). For select patients (e.g., ongoing medical procedures, serious complications, medication dependence, injuries associated with psychological trauma), longer supervised psychological/psychiatric treatment may be justified. Adjunctive treatment generally includes medication for another condition (e.g., depression) as indicated. CBT should normally be limited to 6 sessions or less initially. Additional appointments are generally needed, especially for those with multiple complex problems to address. Provision of additional appointments should be contingent on compliance with the requirements from the initial set of appointments. When therapy is provided as a component of an interdisciplinary or functional restoration program, the number of sessions is based on the needs of the program to provide relevant treatment objectives.
Indications for Discontinuation:	Noncompliance, failure to obtain functional or behavioral improvement, cognitive impairment or low literacy prevents the patient from benefitting from the CBT protocol, or resolution of problems.
Rationale:	There are many moderate quality trials of CBT and combinations of CBT with physical therapy and other interventions. Efficacy of CBT is suggested by a large majority of the quality studies with improvements in pain and function [71, 82, 1405, 1406] [1407] [935, 1408] [1409-1412]. One trial suggested signification

reductions in disability attributed to a combination of CBT and physical therapy [71].

There is no quality evidence to support the use of psychotherapeutic techniques which are not primarily behavioral or cognitive-behavioral in nature in the treatment of patients with chronic nonmalignant pain. While CBT is sometimes used alone, its use in combination with other interventions is recommended [71, 82] [1405, 1406] [935, 1407, 1408] [1410, 1413] [1412]. CBT is not invasive, has negligible adverse effects, is moderate cost in aggregate, has evidence of efficacy and thus is recommended for management of many, if not most patients with subacute or chronic pain conditions.

Evidence: *A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: Cognitive Behavioral Therapy; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic, systematic review, retrospective, and prospective studies. We found and reviewed 599 articles in PubMed, 270 in Scopus, 82 in CINAHL, 9,622 in Cochrane Library, 22,200 in Google Scholar, and 37 from other sources. We considered for inclusion 16 from PubMed, 3 from Scopus, 2 from CINAHL, 0 from Cochrane Library, 5 from Google Scholar, and 37 from other sources. Of the 63 articles considered for inclusion, 58 randomized trials and 5 systematic studies met the inclusion criteria. There is one-high quality study and moderate-quality studies incorporated into this analysis. [904, 907, 909, 918, 919, 921, 923-927] There is low-quality evidence listed in Appendix 4. [897, 928, 935]*

Fear Avoidance Belief Training

Recommended.

Fear avoidance belief training (FABT) is recommended for treatment of patients with acute, subacute and chronic pain.

Strength of Evidence – **Recommended, Evidence (C)**

Indications: All stages and phases of acute to chronic pain. FABT is particularly indicated at the time a patient is voicing a belief. It is also indicated at any point when there is a FAB that is uncovered in routine discussions. Preemptive training is also indicated in the event the worker does not voice the FAB. FABT is generally combined with, and/or addressed in the course of other treatment.

Benefits: Improvement in functional recovery, including exercise compliance. Better ability for the patient to self-actualize. Improved abilities to manage subsequent exacerbations or recurrences.

Harms: Negligible.

Frequency/Dose/Duration: Intervention is provided at the time a FAB is voiced or uncovered. Should particularly address a de-emphasis on anatomical abnormalities, encouraging active management by the patient and education. When a FAB is identified, subsequent vigilance on the part of the provider may help to reinforce proper beliefs and then would usually consist of 2 to 3 appointments and could range up

	to a total of approximately 6 appointments. Patients with particularly strong FABs may require up to 12 appointments.
Indications for Discontinuation:	Resolution of FABs.
Rationale:	FABT has been evaluated in acute, subacute, and chronic pain patients, most of whom had spine pain (Beltran-Alacreu 15; Linton 08; 1217, 2334, 2335, 2338, 2339]; Monticone 14). The one study of acute LBP that included FABT found those with elevated FABs benefitted. [2334] The other studies also suggest that those with elevated fear avoidance beliefs (FABs) benefited from the intervention [614, 2334-2337] [1348] with one exception – that exception was in Norway among individuals on disability pensions, thus applicability to the U.S. or to acute, subacute, or even chronic LBP settings is questionable. [2308] Those with elevated FAB are particularly successfully treated with these interventions, while those without may not benefit. FABT is not invasive and has no adverse effects. FABT is moderate cost as a sole intervention, but low cost for educational information in addition to other provider visits. Thus, FABT is recommended for acute, subacute, or chronic pain patients with elevated FABs at baseline.
Evidence:	A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar, and PsychInfo without date limits using the following terms: fear avoidance belief training; chronic pain, neuropathic pain, radicular pain, psychometric, validity, reliability, disability index, questionnaire. We found and reviewed 2 articles in PubMed, 33 in Scopus, 0 in CINAHL, 16 in Cochrane Library, 24,400 in Google Scholar, and 9 from other sources. We considered for inclusion 1 from PubMed, 1 from Scopus, 0 from CINAHL, 0 from Cochrane Library, 2 from Google Scholar, and 9 from other sources. Of the 12 articles considered for inclusion, 11 randomized controlled trials and 0 systematic study met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. [1217, 2334, 2335, 2338, 2339] (Beltran-Alacreu 2015, Linton 2008) There is low-quality evidence listed in Appendix 4. [2340] (Flink 2016, Wood 2008)

Biofeedback

Biofeedback is a behavioral medicine method to treat conditions by teaching self-awareness of specific sensory sensations and functions, and through this to be able to gain control over bodily processes that are typically thought of as being involuntary [1414-1417] [1418-1422]. Biofeedback has been used for numerous conditions, including hypertension, stress management, temporomandibular joint pain and incontinence.

Biofeedback is theorized to be efficacious by providing means for the patient to gain control over these functions, especially muscle tenseness regarding LBP or other skeletal pain may be reduced and the patient may gain a feeling that pain is a manageable symptom. Biofeedback obtained its name since the patient receives specific feedback of body functions typically through visual or auditory stimuli. For example, the warmth of the finger is measured with a surface temperature probe. A graphic representation may be fed to a computer monitor, and the patient can learn to warm the digits, indicating a decrease in autonomic nervous system arousal. Other examples of physiological processes that can be trained with biofeedback include brain waves (e.g. neurofeedback), skin conductance (e.g. hand perspiration), respiratory rate, and heart rate variability (to modify baroreflex activity and parasympathetic "braking"). For purposes of LBP, the most typical biofeedback modality is surface electromyogram (SEMG), in which muscle activity is measured and fed back to the patient and therapist through a visual display or audible signal, although respiratory biofeedback has also been used.Through this

feedback, the patient can gain increased awareness of excess muscle tension, muscle inhibition during movements and exercises, and postural imbalances, which may be contributing to decreased function and increased pain. Through training and practice, patients can learn to modify dysfunctional muscle habits and to control the degree to which the muscles are contracted or relaxed. Relaxation has been reported to be associated with functional restoration program outcomes. [564, 2341, 2342] Adherents further believe that the training may alter work habits to reduce involvement of injured structures and avoid further injury. [110)

Biofeedback

Recommended.

Biofeedback is recommended for select treatment of chronic pain.

Strength of Evidence – **Recommended, Evidence (C)**
Level of Confidence – **Low**

Indications:	Chronic pain patients who have been treated and compliant with aerobic and strengthening exercises, NSAIDs, etc., with ongoing significant impairment needing multidisciplinary rehabilitation. Biofeedback also is a reasonable as an intervention for patients who also have significant stress-related issues combined with chronic pain. Biofeedback requires motivated and compliant patients and is often performed in conjuction with other self-regulation strategies (e.g., relaxation training, mindfulness meditation, self-hypnosis,. May be of greater benefit for those thought to have muscle tension, stress and/or anxiety.
Benefits:	Improvement in stress management, anxiety, and functional recovery, including exercise compliance. Better ability for the patient to self-actualize. Improved abilities to manage subsequent exacerbations or recurrences.
Harms:	Negligible.
Frequency/Dose/Duration:	Requires a series of appointments to teach techniques and verify appropriate use, generally starting with 5 to 6 appointments. Appointments also needed to reinforce home use. Should generally be used to subsequently enhance functional gains, e.g., increasing activity or exercise levels. May require up to 12 appointments.
Indications for Discontinuation:	No significant improvement after up to 5 to 6 appointments.
Rationale:	There are several moderate quality studies evaluating biofeedback for pain treatments, most of which assessed treatment of chronic LBP and fibromyalgia (Mehling 05). The two highest quality studies suggest modest efficacy for treatment of back pain [1423] and fibromyalgia [1424], although the remainder of the moderate quality studies conflict regarding efficacy [1425-1427]. There are numerous low quality RCTs. There also is no significant quality evidence of efficacy among patients with acute or subacute LBP or radicular pain syndromes. Biofeedback is not invasive, has negligible adverse effects, is moderate cost, has some evidence of efficacy, with the two highest quality studies suggesting modest efficacy. Biofeedback is recommended for treatment of select patients.
Evidence:	*A comprehensive literature search was conducted using PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar without date limits using the following terms: biofeedback, respiratory biofeedback, HRV biofeedback, heart rate variability biofeedback; chronic pain, neuropathic pain, radicular pain, radiculopathy, peripheral neuropathic pain; controlled clinical trial, controlled trials, randomized controlled trial, randomized controlled trials, random allocation, random*, randomized, randomization, randomly; systematic,*

systematic review, retrospective, and prospective studies. We found and reviewed 174 articles in PubMed, 3,646 in Scopus, 11 in CINAHL, 14,100 in Google Scholar, and 3 from other sources. We considered for inclusion 4 from PubMed, 1 from Scopus, 2 from CINAHL, 0 from Cochrane, 2 from Google Scholar, and 14 from other sources. Of the 23 articles considered for inclusion, 20 randomized controlled trials and 2 systematic reviews met the inclusion criteria. There are moderate-quality studies incorporated into this analysis. [732, 2274, 2291, 2343, 2346, 2348]. There is low-quality evidence listed in Appendix 4. [2296, 2349, 2355]

Diagnostic Evidence Tables

Beck Depression Inventory

Evidence for Beck Depression Inventory										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Bishop, 1993 (score=4.5)	Beck Depression Inventory	Diagnostic	Sponsored by Royal Ottowa Health Care group, no mention of COI.	N=113 patients with CLBP.	Mean age: 40.7 years; 61 males, 52 females.	Chronic lower back pain	All patients participated in a multidisciplinary evaluation including BDI, MPQ, and Melzack.	Cut off at 10 yielded a specificity of 0.42 and 0.6. Cut off of 15 shows sensitivity of 0.80 and specificity of 0.70. Cutoff scores above 15 shows sensitivity below 0.80.	"Early intervention may decrease the negative impact of depression on the chronic pain experience and reduce the development of high levels of depression-related disability behavior."	Data suggest screening for depression in chronic pain patients.

Multidimensional Pain Inventory (MPI) or Westhaven Yale Multidimensional Pain Inventory

Evidence for Multidimensional Pain Inventory (MPI) or Westhaven Yale Multidimensional Pain Inventory										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Etscheidt, 1995 (Score = 4.0)	MPI	Diagnostic	No mention of sponsorship or COI.	N = 86 with chronic pain.	Mean age 43.2 years: 39 males and 47 females.	Psychopathology for chronic pain	All completed: Minnesota Multiphasic Personality Inventory (MMPI)	For those classified as Dysfunctional / and Interpersonally Distressed 78.6% and 62.5% evidenced psychopathology based	"For those who presently utilized the MPI, the findings suggest that those patients classified as	Data suggest the MPI components of emotional cognitive interpersonal and behavioral

							and Multidimensional Pain Inventory (MPI)	on occurrence of two-point code-type vs 22.7% of those classified as Adaptive Copers, ($p < 0.0002$).	Dysfunctional or Interpersonal Distressed are more likely to have difficulty with psychopathology than those classified as Adaptive Copers."	
Hopwood, 2008 (Score = 4.0)	MPI	Diagnostic	No mention of sponsorship or COI.	N = 230 with chronic pain.	Mean age 48.58 (10.96): 64 males and 166 females.	Primary diagnoses: lumbar spine with radicular symptoms (46.4%): cervical pain: (16.1%), or fibromyalgia (6.0%).	CARF accredited 4-week treatment program, includes: physical therapy + aquatics + cognitive-behavioral psychotherapy + occupational therapy + individual biofeedback and counseling + and vocational services as needed. INSTRUMENTS: Multidimensional Pain Inventory (MPI) used to classify patients into three clusters or its nine scales (Pain sensitivity, interference, Life Control, Affective Distress, Support, Punishing Responses,	MPI and PAI scores across 4 classifications; Dysfunctional / Interpersonally Distressed / Adaptive Coper / and Repressor: Pain intensity, $R^2 = 0.32$, [57.21^1 (6.41) / 50.76^2 (9.46) / 44.01^3 (9.99) / and 55.85^1 (6.70)]: Interference, $R^2 = 0.22$, [(57.19^1 (5.57) / 54.45^2 (6.67) / 49.82^3 (5.65) / and $55.51^{1,2}$ (4.14)].	"This finding suggests the need for research that focuses on other factors that predict functioning (e.g., medical factors) and treatment outcome (e.g., amenability to change)."	Data suggest dimensional MPI modules consistently outperforms cluster modules.

							Districting Responses, and General Activity Level) / Personality Assessment Inventory (PAI) / Standard Intake and Post-Treatment Questions / Rand 12-Item Short-Form Health Survey (SF-12) / Oswestry Low Back Pain Questionnaire (OLBPQ)			
Verra, 2012 (Score = 4.0)	MPI	Diagnostic	Sponsored by AA. No COI.	N = 204 with chronic musculoskeletal pain (82% chronic non-specific back pain).	Mean age 46.8 years: 59 males and 145 females.	Diagnosis chronic back pain 82 %, Fibromyalgia 15%, Other 3%	Pain management program (=retest) using Multidimensional Pain Inventory scale scores 7 out of 8 between 0.76 and 0.86	Average 4-week time interval for the mean MPI scale scores between ICC = 0.72 and 0.87. Less favorable score was only for MPI scale life control was ICC = 0.57. After 4-weeks 82% in MPI cluster interpersonally distressed (k = 0.69) / 80% of adaptive copers (k = 0.58) / and 75% of dysfunctional patients (k = 0.70). Overall, 78% had stable MPI.	"Test-retest reliability of the German Multidimensional Pain Inventory was moderate to good and comparable to other language versions."	Data suggest MPI classification system is reliable in patients with chronic musculoskeletal pain.

Tests of Malingering Memory

Evidence for Tests of Malingering Memory										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Aguerrevere, 2008 (Score = 5.5)	Tests of Malingering Memory	Diagnostic	No mention of sponsorship or COI.	N = 514 with chronic pain.	Mean age for TBI in definite MND 40.9 (3.3) and probable 39.8 Mean age for chronic pain in probable and definite MND 41.6 (8.4) and 19.4 (1.1): gender not specified.	Chronic pain Neuropsychological (N = 314, N = 185 TBI and 129 general clinic referrals) or pain psychological (N = about 200) Possible (N = 80) and Definite Malingered Neurocognitive Dysfunction or MND (N = 14)	MMPI-2 Infrequency (F) Included 7 different scales: Infrequency-psychopathology (Fp) / Fake Bad Scale / Dissimulation revised (DS-r) / F minus K (F – K raw) / Obvious minus Subtle (O – S raw) / Ego Strength (ES)	In TBI, the original Meyers Index (AUC = 0.780, SE = 0.034) vs Abbreviated Meyers Index (AUC = 0.781, SE = 0.034) significantly differentiated MND from Not-MND patients, ($p < 0.001$). In chronic pain, Meyers Index (AUC = 0.923, SE = 0.031) vs abbreviated Meyers Index (AUC = 0.923, SE = 0.028) significantly differed MPRD from non-MPRD patients, ($p < 0.001$).	"These findings demonstrate that the abbreviated Meyers Index can be used as a substitute of the original Meyers Index without decrements in classification accuracy."	Data suggest there is high accuracy between abbreviated Meyers validity index scale had high diagnostic accuracy in detecting malingering.
Schmand B, 1998 (score=4.0)	Tests of Malingering Memory	Diagnostic	No mention of sponsorship or COI.	N= 174 patients with whiplash non-malingering, whiplash	Mean age: 37.45 years; 74 males, 100 females.	Non-malingering and malingering patients after whiplash, patients after closed	The Amsterdam short term memory (ASTM) test and Dutch adult reading test (DART)	The prevalence of underperformance, as defined by a positive score on the malingering test, was 61% (95% CI:	"The cognitive complaints of non-malingering post-whiplash patients are more likely a result of chronic pain, chronic fatigue, or depression."	Data suggest that cognitive under-performance post-whiplash is prevalent, particularly where there is litigation and it is surprised that

				malingering, closed head injury and normal controls		head injury		45–77) in the context of litigation, and 29% (95% CI: 18–40) in the outpatient clinic (p=0.003). Furthermore, the scores on the memory and concentration test of malingering post-whiplash patients (n=43) and non-malingering post-whiplash patients (n=65) were compared with the scores of patients with closed head injury (n=20) and normal controls (n=46). The malingering post-whiplash patients scored as low as the patients with closed head injury on most tests.		cognitive complaints could result from.
Test of Malingering Memory (TOMM)										
Greve, 2009 (score=6.0)	Test of Malingering Memory (TOMM)	Diagnostic	No mention of sponsorship or COI.	N = 604	Mean age: 42.3 years; 385 males, 219 females.	Chronic pain	Different cutoffs of the Test of Memory Malingering (TOMM)	Original cutoffs for TOMM in trial 2 and Retention trial, had 0% false positives (FP) with 37.5% sensitivity. A cutoff created at 5% FP had 48.5% sensitivity, and 99% specificity (for	"The results show that the original TOMM cutoffs are conservative and that higher scores detect more MPRD patients without causing the FP error rate to become unacceptably high."	Data suggest original TOMM cutoff scores are conservative and that increasing the cutoffs detects more MPRD's without increasing false positives.

								Trial 1, 2, and Retention). A cutoff created at 10% FP had 60.2% sensitivity, and 95% specificity (Trial 1, 2, and Retention).		
Crighton, 2014 (score=6.0)	Test of Malingering Memory (TOMM)	Diagnostic	No mention of sponsorship. No COI.	N = 311 patients with and without disability litigations for musculoskeletal injuries and chronic back pain.	Mean age: 47.05 years; 157 males, 154 females.	Musculoskeletal injury and chronic back pain	Modified Somatic Perception Questionnaire (MSPQ) vs Pain Disability Index (PDI)	Significant results were seen for both MSPQ ($p<.001$) and PDI ($p<.005$) for higher scores in participants with definite/probable malingering, pain exaggeration, and possible malingering, compared to patients with litigation incentive but no malingering, and no pain exaggeration.	"In conclusion, both the MSPQ and PDI are effective in differentiating malingerers from legitimate pain patients, although of the two, the MSPQ appears to be the more effective tool in detecting malingered pain in disability settings."	Data suggest both the MSPQ and PDI are good malingering screening tools but MSPQ best for group differentiation. However, one group involved litigation and the other did not.
Etherton, 2005 (Score = 5.0)	Test of Malingering Memory (TOMM)	Diagnostic	No mention of sponsorship or COI.	N = 200 with chronic pain and unambiguous brain injury or no malingering moderate-severe traumatic	Mean age for MND and TBI 42.75 (8.38) and 34.59 (15.42); TBI with 52 males and 17 females and MND 23 males and 12 females.	Chronic pain with Definite MND (N = 55) and TBI (N = 69)	RDS scores vs Test of Memory Malingering (TOMM) score	RDS score of 7 or lower associated with specificity (> 0.90) and sensitivity (up to 0.60). RDS performance: current pain, $r(74) = -0.08$, $p = 0.49$; least pain, $r(58) = -0.05$, $p = 0.73$; worst pain, $r(64) = -0.10$, ($p = 0.45$).	"Thus, the current study supports the use of the RDS in detecting response bias in neuropsychological patients complaining of pain as well as in the assessment of pain-related cognitive impairment in patients whose primary complaint is pain."	Data suggest RDS may detect response bias in patients complaining of pain.

				brain injury (TBI).						
Greve, 2008 (score=5.0)	Test of Malingering Memory (TOMM)	Diagnostic	No mention of sponsorship or COI.	N = 339	Mean age: 42 years; 241 males, 98 females.	TBI vs. chronic pain	Portland digit recognition test (PDRT), test of memory malingering (TOMM), and word memory test (WMT)	The PDRT and TOMM were very specific but failed to detect about 50% of malingerers; the WMT was sensitive but prone to false positive errors. ROC analyses demonstrated comparable accuracy across all three tests. Joint classification accuracy was superior to that of the individual tests.	"The results for the PDRT and TOMM are consistent with those from previous known-groups calibration studies, which suggests that the WMT findings are likely similarly accurate. However, it will be important to do a detailed calibration study for the WMT. The present study also reported joint classification accuracy for all combinations of the three tests. This represents the first head-to-head known-groups comparison of the three SVTs and the first known-groups study ever of the WMT. The findings provide information for selecting among the SVTs and for conservative interpretation of the SVT results for purposes of diagnosing malingering."	Data suggest a combination of tests (PDRT, TOMM and WMT) to detect malingering is superior to any single test.

Iverson, 2007 (score=5.0)	Test of Malingering Memory (TOMM)	Diagnostic	No mention of sponsorship or COI.	N = 54	Mean age: 51.4 years; 4 males, 54 females.	Fibromyalgia (FM)	Testing effects of FM symptoms of depression or pain when taking the Test of Memory Malingering (TOMM).	Participants had mild to severe levels of depressive symptoms (72.2% and 22.2%) high levels of pain severity ($p<0.03$, Multidimensional Pain Inventory), cognitive impairment ($p<0.02$, British Columbia Cognitive Complaints Inventory), perceived disability due to pain and fibromyalgia ($p<0.001$ for each, Oswestry, and Fibromyalgia Impact Questionnaire). These conditions did not affect TOMM scores in Trial 1, Trial 2, and Retention.	"No patients with fibromyalgia scored below the cutoff scores for suspecting poor effort on the TOMM…. These results, combined with the available literature, suggest that pain and depression, singly or in combination, do not cause patients to perform poorly on the TOMM. Essentially, the TOMM should be considered an effortless test of effort."	Data suggest the TOMM is not affected by FM associated symptoms of depression or chronic pain.
Greiffenstein, 2008 (score=5.0)	Test of Malingering Memory (TOMM)	Diagnostic	No mention of sponsorship or COI.	N = 473	Mean age: 41.9 years; 297 males, 176 females.	Chronic or cognitive pain	Word Memory Test (WMT) and Test of Memory Malingering (TOMM)	Results showed that when defining failure of TOMM to be failure in any of the subtest (compared to only failing Trial 2), and failure for WMT when failing any subtest, the agreement rate of the two tests is	"[B]oth the WMT and TOMM produced more similar failure rates. Further analysis showed WMT failed more often than TOMM by the moderate-severe brain injury subsample. Our main conclusion is	Data suggest both TOMM and WMT are almost identical in terms of their predictive abilities.

								77.2%. This includes 13.7% failing the WMT and passing the TOMM, while 9.1% failed the TOMM and passed the WMT. A 4.4% higher rate for the WMT does not make it a more valid test.	that belief in WMT superiority over the TOMM is unfounded."	
Johnson-Greene, 2013 (score= 4.0)	Test of Malingering Memory (TOMM)	Diagnostic	No mention of sponsorship or COI.	N=85 patients with fibromyalgia	Mean age: 48.33 years; 82 females, 3 males	Fibromyalgia	the Word Memory Test (WMT) or the Test of Memory Malingering (TOMM), and an embedded performance validity test, the Reliable Digit Span (RDS).	Three groups were formed based on effort testing: Two PVTs Failed, One PVT Failed, and No PVTs Failed. We also formed three groups based on disability status: On Disability, Applying for Disability, and Not on Disability. A total of 37% of the patients failed one or both PVTs. PVT group analyses were significant for daily pain, weekly pain, and sleep, but not fatigue. Disability status analyses were significant for daily pain, weekly pain, and fatigue, but not sleep.	"[T]he implication of this study is that PVT performance and disability status are associated with exaggeration of non-cognitive Symptoms such as pain, sleep, and fatigue in persons with fibromyalgia. This study reinforces the importance of effort testing when working with medical populations"	Data suggest PVT performance and disability is correlated with pain, fatigue and sleep exaggeration in FM patients.

Greve, 2009 (score= 4.0)	Test of Malingering Memory (TOMM)	Diagnostic	No mention of sponsorship or COI	N= 1032 patients	Mean age: 41.0 years; 710 males, 322 females.	Mild, moderate to severe traumatic brain injury	the Portland Digit Recognition Test (PDRT), Test of Memory Malingering (TOMM), and Word Memory Test (WMT)	The PDRT and WMT were equivalent to one another in the rates of below-chance results, with both yielding more frequent below-chance results than the TOMM. Seemingly more difficult sections of the PDRT and WMT had higher yields than seemingly easier sections. Multiple SVTs were more likely to yield below-chance results than a single test, supporting the use of multiple SVTs in forensic neuropsychological evaluations.	"[I]t is important to recognize that significantly below-chance scores are worse than would be expected from random choice or guessing, as would be seen in people with absolutely no memory of the items. Although significantly below-chance results on a forced-choice SVT are diagnostic of deliberately poor effort, more subtle malingering presentations are at least as frequent and should not be overlooked in the absence of a below-chance finding"	Data suggest use of multiple tests to detect malingering.

Minnesota Multiphasic Personality Inventory 2 (MMPI-2)

Evidence for Tests of Minnesota Multiphasic Personality Inventory 2 (MMPI-2)										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Aguerrevere, 2008 (Score = 5.5)	MMPI-2	Diagnostic	No mention of sponsorship or COI.	N = 514 with chronic pain.	Mean age for TBI in definite MND 40.9 (3.3) and probable 39.8 Mean age for chronic pain in probable and definite MND 41.6 (8.4) and 19.4 (1.1): gender not specified.	Chronic pain Neuropsychological (N = 314, N = 185 TBI and 129 general clinic referrals) or pain psychological (N = about 200) Possible (N = 80) and Definite Malingered Neurocognitive Dysfunction or MND (N = 14)	MMPI-2 Infrequency (F) Included 7 different scales: Infrequency-psychopathology (Fp) / Fake Bad Scale / Dissimulation revised (DS-r) / F minus K (F – K raw) / Obvious minus Subtle (O – S raw) / Ego Strength (ES)	In TBI, the original Meyers Index (AUC = 0.780, SE = 0.034) vs Abbreviated Meyers Index (AUC = 0.781, SE = 0.034) significantly differentiated MND from Not-MND patients, ($p < 0.001$). In chronic pain, Meyers Index (AUC = 0.923, SE = 0.031) vs abbreviated Meyers Index (AUC = 0.923, SE = 0.028) significantly differed MPRD from non-MPRD patients, ($p < 0.001$).	"These findings demonstrate that the abbreviated Meyers Index can be used as a substitute of the original Meyers Index without decrements in classification accuracy."	Data suggest there is high accuracy between abbreviated Meyers validity index scale had high diagnostic accuracy in detecting malingering.
Pérez-Pareja, 2010 (score =5.0)	MMPI-2	Diagnostic	No mention of COI or sponsorship.	N=114 patients with FM, chronic pain, or controls.	Mean age: 47.68 years; 14 males, 100 females.	FM and Chronic pain	Fibromyalgia group: (n=36) vs Chronic pain (n=44) vs Control (n=34) All patients	Fibromyalgia group mean scores both in F (21.66, 95% CI 18.24-25.08) and Fb (15.77, 95% CI 13.30-18.25). F-scale mean differences for chronic pain group (Dm=12.12, p<.0001) and for control group (Dm=14.72, p<.0001). Similarly, for Fb-scales for chronic pain group (Dm=9.68,	"Results indicate that MMPI-2 is a very useful psychometric tool to characterize a specific pattern of responding of fibromyalgia patients, and it is strongly recommended for	Data suggest the MMPI-2 is a valid psychological tool for detecting somatic responses which are characteristic of FM patients.

							participated in MMPI-2.	p<.0001) and control group (Dm=11.68, p<.0001). Fibromyalgia group scored higher than chronic pain group and the control group in all MMPI-2 validity and clinical scales.	bringing light to its clinical assessment."	
Nordin, 2005 (score =5.0)	MMPI-2	Diagnostic	No mention of sponsorship or COI.	N=468 patients chronic pain patients	Mean age: 39.4 years; 161 males, 307 females.	Chronic pain	Male Cluster 1: (n=149) vs Male Cluster 2: (n=12) vs Female Cluster 1: (n=249) vs Female Cluster 2: (n=58)	Cronbach's alpha scores for cluster 1 ranged from .43 Pa to .79 for Pt. Cluster 2 showed a range of .35 for scale K to .83 for Si. Total sample range was .54 L to .9 Pt. Correlations between MMPI-2 validity scales, clinical scales, pain duration and intensity showed a relationship of p<.01 for Hs, D, Hy, and pain duration (.19, .17, .17). Mean duration of pain was 7.3 years.	"The results also indicated a satisfactory internal consistency and a high discriminant validity of the Swedish version of the MMPI-2."	Data suggest good correlation between original MMPI and the MMPI-2.
Meyers, 2002 (score =5.0)	MMPI-2	Diagnostic	No mention of sponsorship or COI.	N=230 patients with malingering chronic pain.	Mean age: 39.7 years; 113 males, 117 females.	Chronic pain	Experiment 1 Group 1: (n=100) vs Group 2: (n=100) Experiment 2 Group 1: (n=30)	The validity scales ≥5 showed 100% specificity, total weighted score had 86% sensitivity.	"The weighted validity scales method was robust enough to account for "emotional distress" and still identify invalid MMPI-2 performance."	Data suggest litigants produce different results from non-litigants, therefore, a combination of profiles to determine the validity of results is supported.
Etherton, 2005 (score = 5.0)	MMPI-2	Diagnostic	No mention of sponsorship or COI.	N = 200 with chronic pain and unambiguous brain injury or no malingering moderate-severe traumatic	Mean age for MND and TBI 42.75 (8.38) and 34.59 (15.42); TBI with 52 males and 17 females and MND 23 males	Chronic pain with Definite MND (N = 55) and TBI (N = 69)	RDS scores vs Test of Memory Malingering (TOMM) score	RDS score of 7 or lower associated with specificity (> 0.90) and sensitivity (up to 0.60). RDS performance: current pain, r (74) = – 0.08, p = 0.49; least pain, r (58) = – 0.05, p = 0.73; worst pain, r (64) = – 0.10, (p = 0.45).	"Thus, the current study supports the use of the RDS in detecting response bias in neuropsychological patients complaining of pain as well as in the assessment of pain-related cognitive impairment in patients whose primary complaint is pain."	Data suggest RDS may detect response bias in patients complaining of pain.

				brain injury (TBI).	and 12 females.					
Taresc avage, 2015 (score =4.0)	MMPI-2-RF	Diagnostic	No mention of sponsors hip or COI.	N=811 patient s with chronic pain.	Mean age: 46.7±12. 6 years; 318 males, 493 females.	Chronic pain	All patients underwent MMPI-2.	MMPI-2-RF showed internal consistency measures of .67 (THD), .9 (EID), with median of .79. Reliability range was from .61 (persecutory ideation) to .9 (demoralization) with median of .77. Internal consistency ranged from .46 (BRF) to .8 (SAV) with a median of .67. Internal consistency range from .65 (PSYC-r) to .8 (NEGE-r) with median of .77. Mean interim scores ranged from .07 (THD) to .19 (EID) with median of .14. Mean interim score ranged from .08 (persecutory ideation) to .28 (demoralization) with median of .13. Mean interim correlations ranged from .09 (ANP) to .43 (SFD) with median of .22. Mean interim correlations ranged from .07 (PSYC-r) to .16 (NEGE-r) with median of .14. SEMs ranged from 3.7 (EID) to 6.1 (THD with median of 4.7; 3.6 (RCd) to 6.9 (persecutory ideation) with median of 5.1.	"Results indicated reliability and validity for most of the MMPI-2-RF substantive scales."	Data suggest the MMPI-2-RF is an appropriate tool for use in low back pain populations.

Treatment Evidence Tables

Cognitive Therapy

Cognitive Behavioral Therapy (CBT)										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Smeets, 2006 (score = 8.0)	Cognitive Behavioral Therapy	RCT	Supported by Zorgonderzoek Nederland/Medische Wetenschappen (ZonMw) Grant No. 014-32-007. No mention of COI.	N = 309 with chronic LBP of >3 months	Mean age: 41.91±9.65; 93 males, and 79 females.	Compared effectiveness of active physical treatment (APT, n = 53), CBT (CBT, n = 58), combination of both (CT, n = 61) with waiting list (WL, n = 51) for 10 weeks. Interventions: 1) APT, aerobic training and 3 dynamic static strengthening exercises; 2) CBT of operant behavioral graded activity training and problem solving	One year	Roland Disability Questionnaire: WL mean±SD (13.88±4.78); mean difference between WL and APT (-2.40, p <0.01); mean difference WL and CBT (-3.05, p <0.01); mean difference WL and CT (-2.56, p <0.01). Current pain: WL mean±SD (53.35±22.6); mean difference WL and APT (-8.68, p <0.05); mean difference	"[T]he combination treatment integrating physical, graded activity with problem solving training is not a better treatment option for patients with chronic low back pain."	Wait list control bias. Disability/pension status trended to be greater in active PT and combined therapy groups. Duration with limitations greater in cognitive behavioral therapy group. Active interventions appear to be effective.

						training; 3) CT of APT in combination with problem-solving training, both in same frequency and duration. Wait-list control group (WL) after which were offered regular individual rehab treatment.		WL and CBT (-14.76, p <0.01); mean difference WL and CT (-8.23, p <0.05). Beck Depression Inventory (BDI): WL (9.42±7.81); mean difference WL and APT (-2.09, p <0.05); NS between WL and CBT and WL and CT. Global Improvement: WL (3.78±0.91); NS between WL and APT; difference WL and CBT (0.90, p <0.01); difference WL and CT (0.70, p <0.05.		
Wicksell, 2008 (Score=4.5)	Cognitive Behavioral Therapy	RCT	No mention of Sponsorship or COI.	N = 22 with Whiplash-Associated Disorders (WAD)	Mean age 49.15 years: 6 males, 16 females.	Treatment 10 sessions over 8 weeks. Preformed tasks that exposed them with	4 and 7 months	PDI difference between groups (P = 0.003). Treatment group improvement over time,	"These results support findings from previous studies in which a behavior	Waitlist control bias. Data suggest CBT (exposure and acceptance strategies) may improve pain disability,

						increased frequency to behaviors that triggered pain related avoidance. (N = 11) vs Control Standard care (N = 10)		(p = 0.017). SWLS treatment vs control (p = 0.006) improvement between groups at 7 months (P<0.001)	therapy-oriented approach improved functioning in people with chronic pain and WAD."	flexibility, depression and life satisfactions up to 7 months post-treatment.
Linton, 2005 (score = 6.5)	Cognitive Behavioral Therapy	RCT	No mention of sponsorship or COI.	N = 185 with non-specific back or neck pain thought at risk for long-term disability	Mean age: 48.3; Sex: 30 males and 155 females.	Minimal treatment (n = 47) vs. CBT (n = 69) vs. CBT plus PT (n = 69), Minimal treatment consisted of physical exam, information that pain not harmful and resume usual activities, and an information booklet. CBT received minimal treatment plus 6x2-hour CBT sessions including problem solving,	12 month follow-up.	Central tendency and 95% CI for 3 groups. Pre-test vs. follow-up minimal treatment, average pain last week: 5.0 (4.4-5.7) vs. 4.1 (3.3-5.0). CBT group: 4.2 (3.6-4.8) vs. 3.4 (2.8-4.1). CBT+PT: 4.4 (3.9-4.9) vs. 2.9 (2.4-3.5). Average pain last 3 months; minimal treatment: 4.7 (4.3- 5.2) vs. 4.1 (3.3-4.8). CBT: 4.5 (4.0-5.0) vs.	"Adding cognitive-behavioral intervention and cognitive-behavioral intervention and preventive physical therapy can enhance the prevention of long-term disability. There was no substantial difference in the results between the cognitive-behavioral intervention group and	All participants currently employed. CPT plus PT appeared effective in preventing sick leave and chronic disability in patients with non-specific low back pain compared to minimal treatment.

						coping skills and relaxation aimed at preventing problems. CBT plus PT group got additional PT advice on cause of problem and maintaining or resuming activities. Personalized exercise programs included, but don't appear a major component.		3.2 (2.5-3.8). CBT+PT: 4.5 (4.0-4.9) vs. 3.0 (2.6-3.5).	the CBT plus PT group."	
Kashikar-Zuck, 2012 (Score = 6.0)	Cognitive Behavioral Therapy	RCT	Sponsorship by grant from National Institute of Arthritis and Musculoskeletal and Skin Diseases grant. Dr. Passo has received consulting fees, speaking fees, and/or honoraria from Pfizer (less than $10,000). No other COI.	N = 114 adolescents with juvenile FMS.	Mean age; 15 years; 9 males, 105 females.	FM education group; 8-session supportive FM education program. education and discussion about FM, pain medications, general lifestyle issues such as diet, sleep, and exercise, and	8 weeks and 6-month follow-up.	CBT and FM education groups reduction functional disability (main effect for time F = 10.85; P < 0.0001) CBT improvement vs FM education group (group-by-time interaction F = 5.15; P = 0.007)	"…CBT was found to be a safe and effective treatment for reducing functional disability and symptoms of depression in adolescents with juvenile FMS."	Data suggest CBT may be useful for reducing depression and increasing function in chronic musculoskeletal pain in juveniles.

						impact of juvenile (N = 57) vs CBT group; 8-session, individually delivered cognitive-behavioral therapy (CBT) intervention (N = 57)				
Cherkin, 2016 (Score = 6)	Cognitive Behavioral Therapy	RCT	Sponsorship by National Center for Complementary and Integrative Health of the National Institutes of Health. No COI.	N = 343 patients with chronic lower back pain.	Mean age: 49.3; 118 males, 224 females.	CBT: training to change pain-related thoughts and behaviors 8 weekly 2-hour groups. (N = 113) vs MBSR: Training in mindfulness meditation and yoga delivered in 8 weekly 2-hour groups. (N = 116) vs Usual care: (N = 113)	4, 8, 26, 52 weeks.	Improvement in bothersomeness at 26 weeks 43.6% MBSR vs 44.9% CBT group, vs 26.6% usual care group (P = .01). Meaningful improvement on the RDQ MBSR (60.5%) vs CBT (57.7%) vs usual care (44.1%) (overall P = .04)	"Treatment with MBSR or CBT, compared with usual care, resulted in greater improvement in back pain and functional limitations at 26 weeks, with no significant differences in outcomes between MBSR and CBT. These findings suggest that MBSR may be an effective treatment	Usual care Bias Data suggest comparable efficacy between CBT and MBSR for improved back pain and function at 26 weeks compared to usual care.

									option for patients with chronic low back pain."	
Magnussen, 2007 (score = 6.0)	Cognitive Behavioral Therapy	RCT	Funded by Norwegian Foundation for Health and Rehabilitation. No mention of COI.	N = 89 receiving disability pension in Norway	Mean age: 49.1; Sex: 33 males and 56 females.	Intervention had 2 group sessions of 3 hours each separated by 2 to 3 days focusing on spinal problems, mechanisms and reductions in fear avoidance beliefs and 3 additional hours of motivational interviewing (n = 45) vs. control group (n = 44).	One year.	No change in Roland-Morris scores from baseline to 1 year follow-up in either group. No differences in return to work status at 1-year follow-up, but 22% vs. 11% had "entered a return to work process." NS between groups for Norwegian Functional Scale, Fear Avoidance Beliefs Questionnaire- physical activity or work. Life satisfaction (baseline/1 year follow-up): intervention (5.3±1.9/5.3 ±1.7) vs.	"The effort of returning disability pensioners to work by a brief vocational-oriented intervention may be of clinical relevance."	Study of those on disability in Norway. While they called for a larger sample size, results essentially negative. It appears the proportion interested in possibly returning to work is not exactly large and applicability of this intervention to U.S. is questionable.

								control (4.5±1.6/5.4 ±2.0), p = <0.05.		
Linton, 2000 (score = 6.0)	Cognitive Behavioral Therapy	RCT	Supported by theO¨ rebro County Council and the Swedish Council for Work Life Research. COI category: 14.	N =243 with acute and mostly subacute LBP self-identified that felt their problems at risk of becoming a chronic	Mean age: 44.28; Sex: 69males and 173 females.	Pamphlet on back pain; advice on best way to cope with back pain (remain active, think positively); aimed to prevent fear-avoidance, promote coping (n = 70) vs. information package once a week for 6 weeks; based on back school approach (n = 66) vs. CBT of 6 small group sessions for 2 hours once a week for 6 weeks; short reviews to cover homework; structured exercises; new skill development, (n = 107). Intervention	12 months.	A 5-year follow-up evaluation of 97% of the participants found that CBT produced "long-term health and economic benefits. Usual medical care might be improved considerably by implementing these psychologic methods." More sick leave over 5 years in information group (40 vs. 13 days, graphic data interpreted). Risk of long-term disability at the 5-year follow-up was 2.61 times lower in the CBT	"[A] cognitive-behavior group intervention can lower the risk of a long-term disability developing. These findings underscore the significance of early interventions that specifically aim to prevent chronic problems. This approach might be applied to primary care settings."	Number declining intervention at outset 11.9%. Data suggest tendency of subacute LBP to improve over time regardless of treatment, although greater effect among CBT group. Sick leave rates and long-term sick leave risks much better in CBT group.

						6 group sessions.		group. Risk of being on long-term sick disability leave for any illness was 3 times lower. CBT group had significantly less lost productivity, p <0.02. No differences between groups for pain experience or activity level.		
Johnson, 2007 (score = 6.0)	Cognitive Behavioral Therapy	RCT	Supported by the Arthritis Research Campaign, Chesterfield, UK and the Epidemiology Unit at the University of Manchester, UK. No COI.	N = 196 with persistent disabling LBP (>3 months duration)	Mean age: 47.9; Sex: 94 males and 140 females.	Active exercise, education, CBT (n = 116) vs. control (n = 118). Both groups: education booklet and audio-cassette on advice for LBP. Active treatment had group sessions over 6 weeks to develop awareness, focus on resumption of activity,	Follow ups at 3, 9, 15 months	Structured exercises appear to have not been included in homework. Patients who preferred intervention and assigned to it experienced significant reductions in pain and disability scores. Those with preference for controls had worse	"This intervention program produces only modest effects in reducing LBP and disability over a 1-year period. The observation that patient preference for treatment influences outcome warrants further	Magnitude of exercise as described relatively minor and may be a reason for lack of results. Compliance 63% in intervention. Patients had mild LBP at entry. No significant effect found. Co-interventions not well described.

						physical exercise, psychological self-help techniques, encourage return to normal activities/work.		outcomes. For those with no preference, little effect of intervention. No significant differences between groups across 15 months of follow-up.	investigation."	
Karlsson, 2015 (Score = 6.0)	Cognitive Behavioral Therapy	RCT	Supported by grants from the Söderström-KönigFoundation (2003-139), the Swedish Rheumatism Association (51/04), the Swedish Social Insurance Agency (11124), Uppsala County Council (K2003-0036) and Uppsala University (UFV2003/39). No COI.	N = 48 with fibromyalgia syndrome (FMS).	Aged 18 – 64 years; 0 males and 48 females.	Group 1, cognitive behavior therapy treatment (CBT) group (N = 24) vs Group 2, wait-list control group (N = 24).	6-months	For the psychosocial dimension MPI-1 dimension 'life control" scale score: increased in group 1 from 3.15 to 3.62 and decreased to 2.86 in group 2 / 'Pain severity' score: increased from 3.61 to 4.20 in group 1 and decreased to 3.37 in group 2 / and 'Interference' score	"Cognitive behaviour therapy improved the life control in a female population with FMS."	Waitlist control bias. Data suggest CBT improved coping behavior and overall control over life which were maintained at 6 months.

								increased from 3.37 to 4.07 in group 2 decreased to 3.45 in group 2 with a significance of p = 0.01 / 0.02 / and p = 0.04.		
Turner, 2006 (Score = 5.5)	Cognitive Behavioral Therapy	RCT	Supported by the National Institute of Dental and Craniofacial Research Grant. No mention of COI.	N = 158 with chronic temporomandibular pain.	Mean age 38.9 (11.6) and 35.7 (10.9) for PMT and SCM groups; 128 males and 30 females.	Pain management training or PMT assigned to CBT (N = 79) vs Self-care management or (SCM) (N = 79).	3, 6, and 12 months	At 12 months, improvement in pain intensity / masticatory jaw function / and depression: p = 0.01 / < 0.001 / and 0.016 favoring CBT group.	"A brief CBT intervention improves one-year clinical outcomes of TMD clinic patients and these effects appear to result from specific ingredients of the CBT."	Data suggest the one term post intervention clinical outcome of chronic temporomandibular pain are improved with CBT.
Luciano, 2014 (Score = 5.5)	Cognitive Behavioral Therapy	RCT	No sponsorship or COI.	N = 156 with fibromyalgia syndrome (FMS).	Aged 18 – 65 years: 0 males and 156 females.	Acceptance and commitment therapy (ACT/GACT) group, based on one psychotherapy and one pharmacotherapy treatment (N = 51) vs Recommended	6-months	At baseline / After treatment / and at 6-months mean scores comparison for GACT vs RPT vs WL groups on Fibromyalgia impact questionnaire (FIQ): 68.2 (8.96) vs 68.96	"[A] group ACT intervention produces a greater increase in global functional status than recommended medications and no treatment."	Data suggest CBT less costly than either RPT or TAU for treating chronic pain and CBT patients recorded enhanced Q of L.

						pharmacological treatment (RPT) group (N = 52) vs Wait-list or WL group offered preferred therapy (N = 53).		(10.93) vs 65.87 (7.63), (p = 0.22) / 48.70 (6.91) vs 63.37 (9.10) vs 67.68 (9.23) / and 49.49 (8.77) vs 65.11 (8.87) vs 67.45 (9.15).		
Jensen, 2012 (Score = 5.0)	Cognitive Behavioral Therapy	RCT	Supported by the Swedish Society for Medical Research (SSMF) and the Swedish Council for Working Life and Social Research (KJ), Swedish research council, and Stockholm County Council (EK), and the Swedish Rheumatism Association (EK and GO). No COI.	N = 43 with fibromyalgia syndrome (FMS).	Mean age 45.6 (6.4) years: 0 males and 43 females.	Cognitive behavioral therapy or CBT group (N = 25) vs Control group (N = 18).	12-weeks	Patient Global Impression of Change (PGIC) questionnaire in CBT group vs control, (p < 0.01). Pre- to posttreatment correlated with the PGIC responses for the CBT, r = - 0.60, (p < 0.05) and for controls, r = - 0.30, (p = 0.265).	"CBT in patients with FM was associated with increased activity of the vlPFC and OBFC during evoked pain, brain regions implicated in executive cognitive control."	Waitlist control bias. Data suggest CBT changes the processing of chronic brain pain suggesting cortical control theory in response to treatment.
Fersum, 2013 (Score = 5.0)	Cognitive Behavioral Therapy	RCT	Supported by the Norwegian Fund for Post-Graduate Training in Phuysiotherapy and, No COI.	N = 121 with non-specific chronic low back pain for >3 months.	Aged between 18 – 65 years: 73 males	Classification based cognitive functional therapy group (CB-	3 and 12 months	8 out of 59 (13.5%) of the MT-EX group and 1 out of 62 (1.6%) of the	"The classification-based cognitive functional therapy	High dropout in both groups. Statistically significant differences at

					and 48 females.	CFT), 1 hour for 30-45 minute, every 2-3 weeks of a cognitive component, specific movement exercises, daily activities and a physical activity program (N = 62) vs Manual therapy and exercise group (MT-EX), general exercise or motor control exercise of 1 hour for 30 minutes (N = 59).		CB-CFT group were unsuccessful after treatment. CB-CFT group had ODI score of 13.7 points [95% (CI): 11.4–16.1; p < 0.001] and for PINRS scores 3.2 (95% CI: 2.5–3.9; p < 0.001) vs MT-EX group, the mean improvement for ODI score was 5.5 points (95% CI: 2.8–8.3; p < 0.001) and 1.5 for PINRS (95% CI: 0.7–2.2; p < 0.001).	produced superior outcomes for non-specific chronic low back pain compared with traditional manual therapy and exercise."	12 months in favor of cognitive function therapy.
Kristjánsdóttir, 2013 (Score = 5.0)	Cognitive Behavioral Therapy	RCT	Supported by the Research Council of Norway (grant number 182014) (OBK, HE, EE and TLS). No mention of COI.	N = 140 with chronic widespread pain.	Mean age for intervention group 44.59 (11.13) and control group	Smartphone intervention, 1 face-to-face session and 4 weeks of written communication via a smartphone (N = 69)	4-weeks	At 5-month between-group effect sizes for catastrophizing, (p = 0.003) / acceptance of pain, (p = 0.02) / and	"[A] smartphone-delivered intervention with diaries and personalized feedback can reduce catastrophiz	Interventional group had significant drop-outs. Data suggest preliminary evidence support use of smartphone based

					43.80 (11.20): 0 males and 140 females.	vs Control group without a smartphone intervention after the rehabilitation (N = 66).		functioning and symptom levels, (p = 0.001).	ing and prevent increases in functional impairment and symptom levels in women with chronic widespread pain following inpatient rehabilitation."	intervention with diaries and feedback to decrease catastrophizing.
Wetherell, 2011 (Score = 5.0)	Cognitive Behavioral Therapy	RCT	Supported by Grant F4306I from VA Rehabilitation Research and Development Service (J.L.W.). No COI.	N = 114 with chronic nonmalignant pain of any type for at least 6 months.	Mean age 54.9 (12.5) years: 56 males and 58 females.	Acceptance and commitment or ACT with exercise + cognitive fusion + mindfulness + committed actions (N = 57) vs CBT relaxation training + activity pacing + challenging negative thoughts (N = 57).	8-weeks	Pain interference / Depression / and Pain-related anxiety: (b = -0.09, SE = 0.02, p < 0.001 in CBT vs b = -0.06, se = 0.02, p = 0.02) / (Δm = 3.18, t (56) = 3.73, p < 0.001 in CBT vs Δm = -2.32, t (56) = -2.98, p = 0.04) / and (Δm = 5.63, t (56) = 3.02, p = 0.004 in CBT vs Δm = -4.51, t (56) = -3.54,	"In conclusion, this randomized, controlled trial comparing ACT and CBT interventions in an adult sample with chronic nonmalignant pain found evidence of benefits on measures of pain interference and mood in both conditions compared to	Data suggest improved pain interference and mood from both ACT and CBT compared to usual care.

								p < 0.001). r = 0.43, p = 0.001, and correlation with pain acceptance r = 0.12, p = 0.39. vs CBT correlation between changes in interference vs control was r = 0.35, p = 0.008, and correlation with acceptance was, r = 0.103, (p = 0.45).	treatment as usual."	
Monticone, 2013 (Score=5.0)	Cognitive Behavioral Therapy	RCT	No sponsorship or COI	N = 130 Patients after lumbar fusion for degenerative spondylolisthesis and/or lumbar spinal stenosis	Mean age 57.33 years: 51 males, 79 females.	Experimental group: programme consisting of exercises and cognitive-behavioural therapy (N=65) vs Control group: exercise alone (N=65)	Before treatment, 4 weeks after treatment, and 12 months after treatment	ODI linear mixed model. Significant effects of group ($F(1,122.8) = 95.78$, $p < 0.001$) and time ($F(2,120.1) = 432.02$, $p < 0.001$) in favor of the experimental group. Significant group X time interaction effect	"The rehabilitation programme, including the management of catastrophising and kinesiophobia, was superior to the exercise programme in reducing disability, dysfunctional thoughts, and pain,	Data suggest a combination program to manage catastrophizing and kinesiophobia with exercise is better than exercise alone for lumbar spondylolisthesis and stenosis patients post lumbar fusion

								(F(2,120.1) = 20.37, p < 0.001)	and enhancing the quality of life of patients after lumbar fusion for degenerative spondylolisthesis and/or LSS. The effects lasted for at least 1 year after the intervention ended."	
Thieme, 2007 (Score=4.5)	Cognitive Behavioral Therapy	RCT	Sponsored by the Deutsche Forschungsgemeinschaft and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.	N = 125 with Fibromyalgia using ACR criteria	Mean age: 46.55 years; Gender not specified.	CBT (n=42) – Patients received Cognitive-behavioral treatment of 15 weekly 2-hour sessions. Focused on the patients thinking and involved problem solving. vs. OBT (n=43) – Patients received operant-behavioral	12 months.	At follow-up, 53.5% vs. 45.2% vs. 5% reported clinically meaningful improvements in pain intensity ratings. Significant improvements in physical impairments: 58.1% vs. 38.1% vs. 7.5%. Low physical impairment predicted significant decrease in pain intensity.	"Pretreatment patient characteristics are important predictors of treatment response and may serve as a basis for matching treatments to patient characteristics."	Dropout rate in the attention controls (50%) suggests it was not a credible control.

						treatment based on changing observable pain behaviors for 2 hours a week for 15 weeks. vs. Attention placebo (n=40) – Patients participated in general, therapist guided discussion for 2 hours for 15 weeks.		Duration of pain, psychological factors and behavioral factors did not predict reductions in pain.		
Alaranta, 1994 (score = 5.0)	Cognitive Behavioral Therapy	RCT	No mention of sponsorship or COI.	N = 293 with back disease without inflammation, pain duration at least 6 months, age 30-47, no compensation or claim of pension, 1 back surgery at most	Mean age: 40.45; Sex: 133 males and 160 females.	Conventional inpatient rehab (n = 152) vs. program thought to be more active (AKSELI) in Finland (n = 141), 1 year follow-up. AKSELI program 37 hours of guided or self-controlled physical exercises,	3 and 12 months	After 3 months of follow-up, Million disability index decreased more in AKSELI group (17.1 vs. 9.1, p <0.001); 12 months (15.9 vs. 8.9, p = 0.011). Number of annual physician visits also favored AKSELI group	"The intervention program could improve physical disability, but to improve occupational handicap, activities of the whole society (social legislation, labor market policy) are needed."	Applicability to U.S. is unclear. Baseline characteristics minimal. Intensive rehab appears beneficial for chronic LBP patients.

						without passive PT, 5 hours of discussion groups, included cardiovascular endurance exercises. Conventional program included "large amount" of passive PT, including massage, electrical therapies, traction, etc.		(decrease 74% vs. 67%), NS. Mean sick leave days decreased from 57.8 to 33.9 vs. 58.5 to 36.9 in controls, NS.		
Altmaier, 1992 (score = 4.5)	Cognitive Behavioral Therapy	RCT	Supported by a grant from the National Institute for Handicapped Research, No mention COI.	N = 47 age 18-63, admitted over 18-month period to low back rehab program; inclusion criteria disabled/not working due to pain of 3 to 30 months; not candidate for lumbar surgery or involved in personal injury litigation; pain not due to pregnancy or	Mean age: 39.91; Sex: 33 males, and 12 females.	Standard inpatient rehab for chronic LBP (n = 21) vs. psychological program plus standard program (n = 24); 3 week and 6 month follow-up. Standard program consisting of twice daily PT exercise sessions, daily aerobic fitness training, daily	6 months	Return-to-work rate non-statistically significantly lower in psychological group (47.6% vs. 67%). Data revealed that patients improved their overall functioning at discharge and maintained these gains at follow-up assessment; similar	"[T]he psychological treatment failed to add to the effectiveness obtained by the standard rehabilitation program."	As inpatient rehab for LBP, applicability to current US care unclear. Study suggest no additional benefit from providing training in relaxation and coping skills when added to education, support, and exercise programs for chronic low back pain.

				severe vertebral fracture; no significant levels of depression or anger		education classes, and vocational rehab. Psych program included charting of exercise behaviors, contingent verbal praise, relaxation training, biofeedback, and group and individual cognitive-behavioral coping training.		pattern of findings was engaged in active job retraining by follow-up. Patient improvement not differentially affected by treatment group assignment.		
Goossens, 1998 (score = 4.5)	Cognitive Behavioral Therapy	RCT	Supported by a grant from the investigative medicine programme of the Health Insurance Executive Board. No mention of COI.	N = 148 with chronic LBP (>6 months) age 18-65, observable pain behavior, discrepancy between objective clinical findings and pain complaints; partner willing to participate in parallel partner program	Mean age: 39.8; Sex: 53 males and 95 females.	An economic analysis over 3 years to compare treatment with usual care (n = 31) vs. a cognitive program with relaxation 12 sessions of 90 minutes (n = 58) vs. an operant treatment program (n = 59)with a	1 year	Estimated annual costs for these programs were $2,293 vs. $2,119 vs. $3,404 respectively.	"Adding a cognitive component to an operant treatment did not lead to significant differences in costs and improvement in quality of life when compared with the operant treatment alone."	As study conducted in the Netherlands, applicability of economic analysis elsewhere somewhat unclear.

						group discussion.				
Palermo, 2016 (Score = 4.5)	Cognitive Behavioral Therapy	RCT	Supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health. No COI.	N = 273 with chronic idiopathic pain present over the previous 3 months.	Aged 11-17 years: 68 males and 205 females.	Internet-delivered cognitive-behavioral therapy (CBT) group (N = 138) vs Internet education included modules with information about pediatric chronic pain, plus diary and assessments (N = 135).	6-months	From baseline to follow-up, daily activity limitations CBT achieved greater reductions in daily activity limitations vs Internet education group, (b = -1.13, p = 0.03, d = -0.25). After treatment CBT vs internet group for daily activity, b = -0.43, p = 0.39.	"In conclusion, Internet interventions address barriers to access and could ultimately lead to wide dissemination of evidence based psychological pain treatment for youth and their families."	Data suggest a trend towards a benefit from internet delivered CBT for chronic pain adolescents in terms of activities.
Martínez, 2013 (score = 4.5)	Cognitive Behavioral Therapy	RCT	Supported by the Spanish Ministry of Science and Innovation. Author Días-Pierdra supported by grant from the Spanish Ministry of Education. Author Buela-Casal supported by the Spanish	N = 59 who met the 1990 American College of Rheumatology fibromyalgia criteria	59 female, 0 male. Mean age 47.58 years	Both groups participated in 90 minute group sessions (5-6 participants) once each week for 6 weeks. CBT-I program (n = 30) vs Sleep hygiene education	3 and 6 months	CBT-I vs SH changes in sleep quality at pre-treatment, post-treatment, 3 months, and 6 months, respectively. .44, -2.22 ($p<0.05$), -2.02	"Patients in the CBT-I group showed significantly greater changes than those in the SH group in most outcome measures.	Data suggest better improvement in CBT-I group for fatigue, anxiety, depression, pain catastrophizing and daily function.

			Ministry of Science and Innovation and by Spanish Ministry of Education grants.			(SH) group (n = 29)		(p<0.05), 1.27.	The findings underscore the usefulness of CBT-I in the multidisciplinary management of FM."	
Kerns, 2014 (Score = 4.5)	Cognitive Behavioral Therapy	RCT	Supported by Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Clinical Science Research and Development Service Merit Grant, and by the Health Services Research and Development Research Enhancement Award Program. No mention of COI.	N = 128 with chronic back pain.	Mean age 55.5 (13.1) and 55.0 (10.0) for TCMT and SCBT groups: 106 males and 22 females.	Tailored cognitive–behavioral therapy (TCBT) group had 10 weekly sessions, 60-minutes (N = 68) vs Standard CBT (SCBT) group had 10 weekly sessions, 60-minutes (N = 60).	15-weeks	Perception of treatment credibility at end of the first week / after 3 weeks: 8.3 (1.5) vs 8.3 (1.2) / and 8.3 (1.5) vs 8.2 (1.4), F < 1. Treatment engagement and adherence: at 3 sessions completed reported difference between TCBT vs SCBT was x^2 = 0.10, p > 0.10 / and number of cancellations difference between groups, F = 23, (p > 0.10).	"Participants in this study evidenced a high degree of participation and adherence, but treatment tailored to take into account participant preferences, and that employed motivational enhancement strategies, failed to increase treatment participation over and above SCBT for chronic back pain."	"Modified Randomization" used. Data suggest similar adherence to treatment between groups.

Castel, 2012 (Score = 4.0)	Cognitive Behavioral Therapy	RCT	No mention of sponsorship. No COI.	N = 93 with fibromyalgia.	Mean age for Control / CBT / CBT + hypnosis ; 48.7 (6.5) / 50.0 (7.6) / and 6.2): 3 males and 90 females.	Cognitive behavior-therapy (CBT) group (N = 34) vs CBT + hypnosis group (N = 29) vs Control group (N = 30).	3- and 6-months	Post-treatment CBT vs control group at post-treatment on catastrophizing ($p < 0.05$) and sleep index problems ($p < .0001$). At 3-month CTT vs control on psychological distress ($p < 0.05$) / sleep quantity ($p < 0.05$) / and sleep index problems ($p < 0.0001$). Post-treatment CBT + hypnosis vs control on catastrophizing ($p < 0.0001$) / psychological distress ($p < 0.0001$) / and sleep index problems	"This article highlights the beneficial effects of adding hypnosis in a multicomponent cognitive-behavioral group treatment of fibromyalgia patients."	Standard/usual care control bias. Data suggest CBT or CBT plus hypnosis improved symptoms associated with FM.

								(p < 0.0001). At 3-month CBT + hypnosis vs control on catastrophizing (p < 0.05) / psychological distress (p < 0.01) / sleep quantity (p < 0.05) / and sleep index problems (p < 0.0001).		
Glombiewski, 2010 (Score = 4.0)	Cognitive Behavioral Therapy	RCT	Supported by a doctoral thesis scholarship from the University of Marburg. No mention of COI.	N = 128 with chronic back pain.	Mean age 48.8 (11.7): 39 males and 77 females.	Cognitive–behavioral therapy (CBT) group (N = 35) vs Cognitive-behavioral therapy including biofeedback tools (CBT-B) group (N = 31) vs Wait-list control (WLC) group (N = 51).	6-months	CBT-B and CBT equally effective for pain intensity (using, Pain Intensity Questionnaire or PIQ): CBT-B, μ = 0.66 (95% CI 0.39–0.95) vs CBT, μ = 0.60 (95% CI 0.33–0.87)). CBT+CBT-B, 33.85% clinically significantly improved vs WLC 13.73%. Primary outcome PIQ	"In conclusion, biofeedback ingredients did not lead to improved outcome of a psychological intervention."	Waitlist control bias. Data suggest CBT intervention decreased LBP and addition of biofeedback to CBT did not improve clinical outcomes. Not all patients randomized. Not blinded. Pooled CBT arms compared to control had improvements in many subjective measures but clinical

								/ Secondary outcome Pain Diary & RLS Scale & CS Scale & Doctor Visits; F (1.57, 177.98) = 3.45, p = 0.043 / (F (1.9, 133.32) = 1.29, p = 0.28, & F (1.96, 221.12) = 58.73, p < 0.001, & F (1.66, 186.64) = 8.8, p < 0.001).		significance uncertain. Data suggest no benefit from CBT when biofeedback is added.
Lera, 2009 (Score = 4.0)	Cognitive Behavioral Therapy	RCT	No mention of sponsorship or COI.	N = 83 with fibromyalgia (FM) symptoms.	Mean age 50.2 (9.3) years: 0 males and 83 females.	Multidisciplinary treatment or MT + CBT for 15 group sessions, 90 min per week (N = 43) vs Multidisciplinary treatment (MT) group received education about the central nervous	6-months	MT+CBT vs MT at baseline / post-treatment: Fibromyalgia Impact Questionnaire (FIQ) mean score 59.2 (9.6) / 53.2 (13.4) vs 58.4 (10.4) / 57.2 (11.3): Functional Status (FS) means 38.6 (22.1) / 39.5 (20.4) vs 32.3	"In less severe FM patients who also suffer fatigue, the addition of CBT leads to a greater improvement in daily functioning and health status than is achieved through a basic multidisciplinary program	Data suggest MT improved function and symptom impact in FM patients.

						system and the peripheral sensations, different levels of pain processing, behavioral techniques (N = 40).		(17.6) / 30.7 (14.4): Emotional well-being (EW) means: 29.1 (12.4) / 33.9 (14.6) vs 27.1 (13.6) / 28.8 (12.9).	consisting of education, physical training, and medical management."	
Thieme, 2016 (Score = 4.0)	Cognitive Behavioral Therapy	RCT	Supported by grants of the Deutsche Forschungsgemeinschaft to KT Th 877/1-2 and the Bundesministerium f€ur Bildung und Forschung to HF. No COI.	N = 145 with fibromyalgia.	Mean age for OBT / CBT / IH / and CON; 43.24 (9.03) / 49.13 (10.03) / 47.46 (9.75) / and 48.22 (9.02): 0 males and 15 females.	Cognitive behavioural treatment (CBT) group 2-h sessions (N = 42) vs Operant behavioural (OBT) group 2-h sessions (N = 43) vs Whole-body infrared heat (IH) group 2 h-sessions (N = 30) vs Pain-free controls (CON) group 2-h sessions (N = 30).	15-weeks	OBT and CBT vs IH reduced pain intensity [OBT: effect size (ES) = 1.21 CI: 0.71–1.71 vs CBT: ES = 1.23, CI: 0.72–1.74]. At 12 months, OBT increased diastolic blood pressure [ES = 1.13, CI: 0.63–1.63 and CBT reduced SCL (ES) = - 0.66, CI: -1.14–0.18]. CBT vs OBT significantly increased EMG levels (OBT: ES = 0.97, CI: 0.48–1.46, CBT: ES =	"Increased diastolic blood pressure and decreased pain after OBT suggest a reactivation of baroreflex-mechanisms in fibromyalgia and a normalization of the blood pressure and pain functional relationship."	Data suggest OBT and CBT decreased pain but are different mechanisms.

								1.17, CI: 0.67–1.68).		
Ang, 2010 (Score = 4.0)	Cognitive Behavioral Therapy	RCT	No mention of sponsorship or COI.	N = 32 with fibromyalgia (FM) symptoms.	Mean age for CBT / and UC groups, 50.5 ± 9.5 and / 47.0 ± 12.4: 0 males and 32 females.	Telephone-delivered CBT group, 6 weekly sessions (N = 17) vs Usual care (UC) group (N = 15).	6-months	Pre- to 6 months, nociceptive flexion reflex (NFR) mean scores for UC group (4.4 ± 13.7 mA vs -10.2 ± 9.9 mA for CBT, (p = 0.005). And at week 12 NFR mean scores were: (7.3 ± 9.2 mA for CBT vs -5.4 ± 13.5 mA for UC, (p = 0.01).	"Compared with UC, CBT reduced nociceptive responding in fibromyalgia patients."	Pilot study. Usual care bias. Data suggest CBT decreased nociception response in FM patients.
Schweikert, 2006 (score = 4.0)	Cognitive Behavioral Therapy	RCT	Supported by the German Federal Ministry of Education and Research and the Federation of the German Pension Insurance Institutes. No mention of COI.	N = 409 with non-specific LBP of at least 6 months; excluded if severe co-morbidities and indication of sever spinal pathology (e.g., RA, arthritis, osteoporosis, fibromyalgia)	Mean age: 46.7±9.1 ; Sex: 339 males and 70 females.	Intervention (n = 200) vs. usual care (n = 209). Intervention: cognitive-behavioral pain management of 6 group sessions 1.5 hour each plus 1 individual prep and final session (0.5 hour each). Usual	6 months	At 6 months follow-up, intervention group (mean: 11.4, sd: 28.9) absent from work average of 5.4 days less than usual treatment (mean: 16.5, sd: 34.1, p = 0.115). No significant differences in quality-	"The cognitive behavioral treatment showed lower indirect costs."	Use of an inpatient program for LBP may not have generalizability where such treatment is extraordinarily rare (e.g., USA).

						care: standardized conventional 3 week inpatient rehab program of daily physiotherapy in small groups, massage of spinal region, electro-therapeutical measures, 1-hour seminary regarding back training, twice-daily exercise program, seminars on lifestyle and risk factors for back pain and its process of becoming chronic.		adjusted life-years gained or in direct medical or nonmedical costs found between groups.		
Friedrich, 2005 (score = 4.0)	Cognitive Behavioral Therapy	RCT	No sponsorship or COI.	N = 93 with chronic and recurrent LBP	Mean age: 44.12; Sex: 46 males, and 47 females	Standard exercise program (n = 49) vs. a combination of an exercise and motivational program (n = 44) over a 5-	5 years	Effects of motivational group on disability measure present at 3.5 weeks and 4 months (p = 0.003) and	"Regarding long-term efficacy, the combined exercise and motivation program was superior to the	Combined motivational and exercise program thought to reduce disability and pain and increase work ability in

						year period. Dropout rate over 5 years was 40%. Exercise program consisted of ten 25-minute training sessions of individual submaximal gradually increased exercises focused on spinal mobility, truck and lower limb "muscle length," force, endurance and coordination. Motivational program focused on extensive counseling emphasizing importance of regular exercise, reinforcement of techniques used, treatment contracts,		persisted for 5 years. Pain ratings also lower in motivational group, p <0.001 vs. control, p = 0.155. Still apparent at 5 year follow-up, p = 0.0011. LBP episodes requiring therapy lower over 5 years in motivational group. Work ability measures also superior in motivational group, p = 0.005.	standard exercise program. Five years after the supervised combined exercise and motivational program, patients had significant improvements in disability, pain intensity, and working ability."	patients with chronic pain. 40% dropout rate over 5 years. Working ability assessed. Co-interventions not well described. Exercise and motivation reported to increase function in chronic LBP patients without adding additional training time.

						posting of treatment contract in home, and maintenance of an exercise diary. Compliance higher in motivational group.				
Keller, 1997 (score = 4.0)	Cognitive Behavioral Therapy	RCT	No mention of sponsorship or COI.	N = 64 with 1) chronic LBP (Quebec Task Force on Spinal Disorders classification); 2) no previous pain management program; 3) fluent in German; 4) able to attend therapy sessions on a regular basis in an outpatient setting; 5) provided informed consent	Mean age: 47.89; Sex: 18 male, and 45 females	Treatment program (n = 35) vs. wait-list controls (n = 29). Consisted of group meetings and 18 individualized training sessions supervised by physicians, physiotherapists, and pain psychologists. Education and relaxation exercises included.	6 months	Baseline differences NS, but present. Pain frequency, typical pain intensity and disability caused by pain reduced as consequence of treatment. Improvement in daily functioning, although strength and endurance not affected due to strict statistical criteria. Behavioral observations clarify that posture and performance of daily	"These changes corresponded with improvements in well-being, whereas depression scores remained unchanged as before."	Wait list control bias (quantified as 7 refusals to participate after assignment to control group.) Baseline characteristics comparisons were minimal. Co-interventions not well described. Physical activity appears to improve outcomes in chronic LBP.

								activities improved. At follow-up, most improvements reported maintained. T-tests revealed improved scores compared to pre-treatment scores on both pain frequency and typical pain intensity. Changes were accompanied by better daily functioning, and also in contrast to post-treatment findings, by improved strength and endurance. Disability scores unimproved. Observation of posture and behavioral habits		

								confirmed improvements. Ratings of pain related self-efficacy not improved. Patient attitudes towards posture and pain more favorable compared to pre-program value…		
Kole-Snijders, 1999 (score = 4.0)	Cognitive Behavioral Therapy	RCT	Supported by a grant from the Investigative Medicine Fund of the Dutch Insurance Council. No mention of COI.	N = 175 with LBP for at least 6 months, age 18-65, discrepancy between objective findings and pain complaints, and cooperation of spouse	Mean age: 39.8; Sex: 54 males and 94 women.	Complete treatment package (OPCO, n = 59) vs. operant program and group discussion (OPDI, n = 58) vs. waiting-list control (WLC, n = 31). Two measurements before treatment (Pre-treatment 1 and 2, with 2-week interval) and 2 follow-up measurements, at 6	Follow up at 6months and 1 year post treatment.	Less pain behavior and higher pain coping and pain control $\chi 2$ (2, N =149) >=17.4, p<.001. Calculation of improvement rates revealed that OPCP and OPDI had significantly more improved patients than OPUS on all the dependent variables (p = 0.01)".	"Compared with WLC, both OPCP and OPDI led to less negative affect, higher activity tolerance, less pain behavior and higher pain coping and pain control. At posttreatment, OPCP led to better aim coping and pain control than OPDI. Calculation of improveme	Dropout rate for follow-up measurements was high and compliance low. Dropout rate >20% Cognitive behavioral interventions are reported to help in patients with chronic low back pain compared to wait listing.

						(Follow-Up 1), 12 months (Follow-Up 2) after termination of treatment. Of 148 who started measurements, results available for 133 post-treatment and 107 at follow-up. OPCO received operant behavioral treatment and cognitive coping skill training. Cognitive received education that hurt does not necessary mean harm. Electromyography biofeedback used to help patients recognize changes in tension and relaxation. Control waiting-list			nt rates revealed that OPCP and OPDI had significantly more improved patients than OPUS on all the dependent variables."	

						group received no treatments.				
Other Psychological Therapies										
Luciano, 2014 (score = 6.5)	Other Psychological Therapies	RCT	No COI. Author Luciano was given a research contract form the Institute of Health Carlos III.	N = 156 who fulfilled the 1990 American College of Rheumatology criteria for fibromyalgia	Mean age: GACT 49, RPT 51, WL 50; 6 males, 150 females.	Group Acceptance and Commitment Therapy (GACT) – 2.5 hour sessions involving ACT and mindfulness practice, 8 sessions total (n = 51) vs Recommended pharmacological treatment (RPT) – pregabalin (300-600 mg/day), duloxetine (60-120 mg/day) for those who had major depression (n = 52) vs Waitlist control (WL) (n = 53)	3 and 6 months	FIQ total scores (0-100) at baseline, post-treatment, and 6 month follow-up, respectfully: GACT 68.20, 48.70, 49.49, RPT 68.96, 63.37, 65.11, WL 65.87, 67.68, 67.45 (F=3.32, p=0.036).	"Changes in pain acceptance only mediated the relationship between study condition and health-related quality of life. These findings are discussed in relation to previous psychological research on FM treatment."	Data suggest group acceptance and commitment therapy (GACT) statistically superior to recommended pharmacological treatment (RPT) and waitlist (WL) both immediately after treatment and at 6 months. Waitlist control bias.
Buhrman, 2013	Other Psycholo	RCT	Supported by a grant	N = 76 with chronic pain.	Mean age 49.1 (10.34)	Acceptance and commitment	7-weeks	Chronic Pain Acceptance Questionnair	"[A]n acceptance based internet delivered treatment	Medication use not described.

(Score = 4.5)	gical Therapies		From Linköping University, a grant from Rehsam / Vårdalsstiftelsen, and the Swedish council for working and life research. No COI.		years: 31 males and 45 females.	therapy (ACT) group of 7-sections (N = 38) vs Control group participated in moderated online discussion forum (N = 38).		e (CPAQ): at 6-months t (28) = 0.29 – 1.95, (p = 0.77 – 0.06). Means CPAQ pre vs post; 22.84 (11.02) and 21.18 (9.70) for treatment and control vs 28.62 (11.15) and 22.22 (11.17) for treatment and control, (F-u M (SD) = 27.51(11.60) .	can be effective for persons with chronic pain."	Data suggest internet-delivered acceptance and commitmen t therapy may benefit chronic pain patients.
La Cour, 2015 (Score = 4.0)	Other Psycholo gical Therapies	RCT	Supported by TrygFonden, Axel Muusfeldts Fond, Fabrikant Mads Clausens Fond, and Fonden af 1870. No COI.	N = 109 with nonspecific chronic pain.	Mean age 46.52 (12.42) / 48.84 (12.20) for meditati on / WL groups: 16 males and 93 females.	Meditation group included mindfulness program (N = 43) vs Control or wait list (WL) group (N = 47).	6-months	SF36 "vitality" dimension after intervention, ($p \leq 0.05$). Score for the SF36 questions about the impact of pain on everyday life between baseline raw score mean 2.07 (0.89) and after the course mean 2.57 (SD	"A standardized mindfulness program (MBSR) contributes positively to pain management and can exert clinically relevant effects on several important dimensions in patients with long-lasting chronic pain."	Waitlist control bias. Baseline differences in agreed duration of pain. Significance dropout rate matching conclusions difficult but data suggest MBSR may benefit chronic

								1.13), p = 0.01 and after 6 months mean 2.71 (1.18), (p < 0.01).		pain patients.

Fear Avoidance Belief Training (FABT)

Evidence for Fear Avoidance Belief Training (FABT)										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
George, 2003 (score = 7.5)	Fear Avoidance Belief Training	RCT	Support for this study provided by Foundation for Physical Therapy. No mention of COI.	N = 66 with acute LBP within 8 weeks of study.	Mean age: 38.19; Sex: 28 males and 38 females.	Fear avoidance physical therapy (n = 34) vs. Standard physical therapy (n = 32) for duration of 4 weeks. Median number of therapy appointments 6 for both groups.	Final follow-up at 6 months.	Between group differences (95% CI)/p values for fear avoidance beliefs questionnaire at 4 weeks, and 6 months: 4.2(1.3 to 7.1)/p = 0.006, 3.4(0.2 to 6.6)/p = 0.037.	"[D]isability experienced at 4 weeks and 6 months after an episode of low back pain is dependent on an interaction between the type of treatment received and the level of fear-avoidance beliefs."	Most (62%) also had lower extremity pain. Non-significant differences favoring FABT over standard treatment at 4 weeks and 6 months. Treatment found to be beneficial for those with elevated baseline FABs.
Sorensen, 2010 (score = 7.0)	Fear Avoidance Belief Training	RCT	Supported by grants from IMK Foundation, Health Insurance Foundation, Tryg Foundationen,	N = 207 with LBP at least 4 of prior 12 months, a mean LBP score over last	Mean age: 39; Sex: 99 males and 108 females	Educational group (EDUC, n = 105) had 1-3wk intervals, 1st and 3rd by TB.	Follow-up at 2, 6, and 12 months.	No differences between groups for pain and activity limitations, physical activity, and work ability. FAB	"A cognitive, educational intervention for cLBP resulted in at least as good outcomes as a	Patient contact bias in favor of traditional PT, suggest alternate

			Funen County Research Foundation and Danish Rheumatism Association. Authors declare no competing interests.	14 days of ≥4 (scale 0-10), and back pain had to be greater than any associated leg pain.		2nd visit a group visit, included a relative. 2nd visit led by PT with experience in chronic pain mgt. Also gave PowerPoint to study general biology and cognitive aspects. Symptom-based physical training program (TRAIN, n = 102) had consultation at 1st visit with PT for possible direction of preference exercises, plus advice on optimal postures.		Questionnaires differed (2 mos: EDUC = 10.3 ± 5.9 vs. TRAIN = 13.3 ± 6.4, p < .001; 6 mos: EDUC = 10.8 ± 6.2 vs. TRAIN = 13.3±6.0, p = 0.007, 12 mos: EDUC = 10.5 ± 6.1 vs. TRAIN = 13.1±6.5, p = 0.01), and Back Belief Questionnaire at 6 mo. (EDUC: 24.3 ± 12.7 vs. TRAIN: 28.5 ± 11.4, p = 0.01)	symptom-based physical training method despite fewer treatment sessions."	treatment may be superior. Mostly subacute to chronic pain population.
Beltran-Alacreu, 2015 (Score=6.0)	Fear Avoidance Belief Training	RCT	No sponsorship or COI	N=45 with nonspecific chronic neck pain.	Mean age 41.4 years: 20 males, 25 females	All received 8 treatments over 1 month (2 per week) Control Manual therapy (MT) (N=15) vs	4, 8, 16 weeks.	Nonparametric Kruskal-Wallis test of neck disability index difference of baseline and follow up periods (p < 0.01) Difference for Visual Analog Fatigue scale &	"Differences between experimental groups and the control group were found in the short and medium term. Multimodal	Small sample size, all received manual therapy. Multiple co-interventions. Data suggest FABT most important

						Group 1 Received MT and therapeutic patient education (TPE) (N=15) vs Group 2 Received MT, TPE, and therapeutic exercise protocol. (N=15)		Neck Flexor Muscle Endurance test at 8 and 16 weeks ($p < 0.05$) Variance for group X time interaction ($P = 0.005$). Fear Avoidance Beliefs Questionnaire ($P = 0.022$).	treatment is a good method for reducing disability in patients with nonspecific chronic neck pain in the short and medium term."	component as little additive benefit from this exercise regimen for improving the disability associated with non-specific CNP. Both groups received education which included FABT.
Jay, 2016 (score=5.5)	Fear avoidance belief training	RCT	No mention of sponsorship. No COI.	N = 112 patients with chronic musculoskeletal pain	Mean age: 46.55 years; 0 males, 112 females.	Physical-cognitive mindfulness training intervention group, including joint mobility, strength training, and CBT for 20 min 4X/week, and mindfulness group training 1Xweekly (PCMT, N = 56) vs reference group, which followed company initiatives of ergonomic education and	Follow-up at baseline and 10 weeks.	Significant results were seen in a group by time interaction in work-related Fear-Avoidance Beliefs for the PCMT group ($P<0.05$) at the 10-week follow-up.	"[A] 10-week targeted physical-cognitive mindfulness intervention has significant effects on work-related FAB. As previously reported, the intervention group experienced reduced pain intensity by ~52% across 6 body regions compared to the REF group"	Data suggest work-related fear avoidance beliefs may be reduced by 10 weeks with PCMT training in female chronic pain patients.

						10 minute exercise breaks 3X/week (REF, N = 56)				
Pfingsten, 2001 (score = 4.5)	Fear Avoidance Belief Training	RCT	Study was supported by Deutsche Forschungsmeinschaft Grant. No mention of COI.	N = 50 with non-specific CLBP	Mean age: 41.4 ±1.5; Sex: 27males and 23 females.	Anticipating pain (n = 25) vs. Anticipating no pain (n = 25) while being tested for leg flexion movement.	None.	Anticipating pain vs. anticipating no pain intensity of pain mean±SD at time before instruction, time after instruction, and time after behavioral test: 38.2±20.2/38.1±20.7, 45.9±21.8/28.6±18.9, 48.1±23.7/30.2±19.6. Fear: 40.3±21.4/41.8±20.5, 46.5±20.1/27.4±23.3, 43.6±18.5/26.2±21.9.	"Results confirm that pain anticipation and fear-avoidance beliefs significantly influence the behavior of patients with low back pain in that they motivate avoidance behavior."	Controls informed it would not result in pain. Patients anticipating pain performed more poorly than those who did not anticipate pain.
Klaber Moffett, 2004 (score = 4.5)	Fear Avoidance Belief Training	RCT	Other funds received in support of this work. No COIs.	N = 187 with mechanical LBP between 6 weeks and 6 months	Mean age: 41.88; Sex: 81 males, and 106 females.	Exercise (8 1-hour session spread over 4 weeks vs. Usual care. Exercise intervention with low impact aerobics, strengthening, and stretching exercises	Final follow-up at 12 months.	Outcomes compared at 6 weeks, 6 months, and 12 months. High fear-avoiders fared significantly better in exercise program than usual care at 6 weeks and 1 year; low fear-avoiders did not. Distressed or depressed patients significantly better off at 6 weeks, but benefits not	"Patients with high levels of fear avoidance beliefs could significantly benefit from the Back to Fitness program. The benefits of the exercise program for patients with high levels of distress/depression appear to be short-term only."	Attendance suboptimal and averaged 4-5 classes. Comparison group underwent treatment by GP in U.K., thus likely heterogeneous and may have included individuals not optimally treated, thus

								maintained long-term.		potentially magnifying results which generally favored exercise, particularly including in high FAB group at up to 12 months.
Linton, 2008 (Score=4.0)	Fear Avoidance Belief Training	RCT	No mention of sponsorship or COI.	N = 46 patients with long-term back pain and reduced function who are fearful according to standardized measures.	Mean age 47.85 years: 16 males, and 18 females	All received usual treatment according to their medical plan. Exposure 13-15 sessions where 8-10 were graded exposure in vivo sessions. (N = 13) vs Waiting list control (N = 21)	3 months	WLC-TAU group (29%) either had no improvement or had deteriorated on the TSK versus (0%) in the EXPOSE-TAU group (p = 0.03) ADL (no improvement: 38% WLC-TAU, 9% Exposure) (p = 0.08)	"Compared to a group receiving usual treatment and waiting for exposure, the exposure in vivo group demonstrated significantly larger improvement on function. Overall exposure had moderate effects on function, fear and pain intensity. We conclude that exposure may be important in treatment, but is not recommended as a ''stand alone" adjunct to usual treatment."	Data suggest exposure group showed improved function but did not improve pain or fear.
Slater, 2009 (score = 4.0)	Fear Avoidance Belief Training	RCT	Supported by Office of Research and Development, Health Services Research and	N = 67 with first-onset back pain (thoracic vertebra 6 or below)	Mean age: 30.52; Sex: 58 males,	Behavioral Medicine Group (BMG, n = 34) had 4 weekly, 1 hour	6 months	At six months, Pain and Impairment Relationship Scale differed (BMG = 50.00 ± 16.20 vs. ACG = 60.60 ±	"A behavioral medicine, rehabilitation intervention applied at the subacute phase	Mostly subacute to chronic pain population. Study defined chronic pain

			Development Service and Medical Research Service, Department of Veterans Affairs. Dr. Atkinson is on Scientific Advisory Board of Eli Lily which sells antidepressants, an alternative treatment method for LBP.	present at least 6 but no less than 10 weeks, and not candidate for acute surgical intervention.	and 9 females.	individual sessions, let by a master's-level clinician trained in study in behavior pain management and rehabilitation method. Attention Control Group (ACG, n = 33) had 4 weekly, 1 hour individual sessions led by a master's-level clinician with training in psychotherapy, and provided nondirective, supportive care.		12.50, p ≤ 0.05). For patients who completed 4 sessions, there was significant difference in those who recovered at 6 months (BMG = 54% vs. ACG = 23%, χ ^2 = 5.12, df = 1, p = 0.02). Recovery rates in the maximum dose sample (n = 32) of those who recovered was significantly higher in BMG (75%) versus ACG (20%, χ^2 = 9.41, df = 1, p = 0.002).	for individuals with first-onset LBP and moderate functional work limitations enhanced recovery and reduced chronic pain and disability at 6 months after pain onset, relative to an attention control condition."	at 6 months post initial onset. Data suggest behavioral interventions may be beneficial in reducing progressions to chronic LBP in military population with 1st onset LBP. Compliance <80% and loss to follow up which author excluded non-compliant.
Rolving, 2014 (score=4.0)	Fear avoidance belief training	RCT	Sponsorship by the Danish Working Environment Research Fund. No mention of COI.	N = 83 patients with non-specific neck pain on sick leave	Mean age: 39.3 years; 23 males, 60 females.	General physical activity at home 3-4 h/week or 30 min/day (GPA, N = 40) vs GPA with additional 15-20 min 3x/week of strength training of the neck and	Follow-up at baseline and 3 months.	Significant pain reduction and increase in neck flexion strength for GPA group (p=0.046, p=0.014 respectively) and SST (p<0.001, p=0.001 respectively) with no significant difference between groups. Improvement of	"The overall pain reduction gained by adding specific strength training to a program of general physical activity was not found to be clinically relevant in the present study. Only limited improvements in muscle strength	Data suggest a trend towards reduced pain in the SST group, both groups improved in neck flexion strength but there was a significant improvement in fear-

						shoulder, (SST, N = 43).		within group Fear-Avoidance Beliefs were seen in both groups (p<0.001 for SST, p=0.004 for GPA) with a significant difference between groups (p=0.046).	were gained with either type of training. Participants of the specific training program did however show an improvement in fear-avoidance belief compared to the participants in the general physical activity program, although a significant within-group improvement was also seen here."	avoidance beliefs in the SST group. Home-based low supervision training does not appear to increase muscle strength or decrease pain.

Biofeedback

Evidence for Biofeedback										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kent, 2015 (score=7.0)	Biofeedback	RCT	Sponsored by dorsaVi P/L and the Victorian State Government. COI, authors, clinicians and patients were reimbursed by the Victorian State	N = 112 patients with chronic back pain.	Mean age: 43.5 years; 51 males, 61 females.	Movement Biofeedback Group (N = 58) vs Guidelines-based Care Group (N = 54). Both groups had 6-8 clinical consultations over 10 wks.	Follow-up at baseline, 3 and 12 months.	Results showed significant improvement in biofeedback group vs. controls in Roland Morris Disability Questionnaire (activity limitation, p<0.014), Patient Specific Functional Scale (p=0.001),	"Patients in the Movement Biofeedback Group showed significant improvements in the primary outcome measures of activity	Cluster randomization. Data suggest changing posture and movement patterns with sensor biofeedback may decrease chronic low

			Government and dorsaVi.			Advice was given on management of LBP, importance of staying active. Based on data received from the ViMove system in Biofeedback Group, clinician would identify and offer suggestions to adjust movement dysfunction related to LBP. Other group had sham biofeedback sensor.		and self-reported pain (VAS scale, p<0.004).	limitation and pain intensity, compared with those in the Guidelines-based Care Group, as seen by the group effects and group-by-time interaction effects all favouring the Movement Biofeedback Group"	back pain and improve activity when compared to sham.
Babu, 2007 (score = 6.5)	Biofeedback	RCT	Supported by Ethical Committee of Christian Medical College and Hospital, Vellore, and Fluid Research Grant. All authors are employees of Christian Medical	N = 30 who met the 1990 American College of Rheumatology fibromyalgia criteria	21 female, 9 male. Mean age 39 years	Biofeedback (n = 15) vs Sham biofeedback (n = 15). Each group received a continuous six-day treatment with each session being 45 minutes long	6 days	Mean changes in baseline scores after 6 days for biofeedback and sham groups, respectively. FIQ -21.9, -12.3 (p=0.05), VAS -4.3, -2.6 (p=0.09), Tender points -8.6, -4.4 (p=0.002), Six-minute walking test distance in meters 69, 16 (p=0.08)	"Biofeedback as a treatment modality reduces pain in patients with FMS, along with improvements in FIQ, SMWT and the number of tender points."	Data suggest biofeedback reduces pain in fibromyalgia patients and positively impacts fibromyalgia impact questionnaires.

			College and Hospital.							
Kapitza, 2010 (score = 6.0)	Biofeedback	RCT	Industry sponsorship (Biomental Gesellschaft fűr Mentalsystem e) and no mention of COI.	N = 42 with moderate chronic LBP at least 3 months and 1 week before study, no change in medication.	Mean age: RFB 21, non-contingent RFB 21; 15 males, 27 females.	Non-invasive relaxation breathing technique or RFB with synchronized feedback (n = 21) vs. RFB placebo, no feedback (n = 21).	2 weeks, 3 months	PDI/recreation/social activity/ sexual life/RI/VAS at rest and during activity; p = 0.004/p = 0.006/p = 0.005/ p = 0.027 / increase of 0.22 points for RFB / p=0.12 & p= 0.01 vs. p = 0.27 and p = 0.014.	"…RFB can be used as a useful, safe and effective adjunct in multimodal pain therapy."	Although authors conclude RFB may have benefit, the study's data show no statistical or clinically significant differences between groups.
van Santen, 2002 (score = 5.5)	Biofeedback	RCT	Supported by the Dutch Arthritis Association. No mention of COI.	N = 129 who met the 1990 American College of Rheumatology fibromyalgia criteria	129 female, 0 male. Mean age fitness group 46.2 years, biofeedback group 44.4 years, control group 42.8 years	Fitness group, exercised for 60 min two times a week for 24 weeks (n = 50) vs Biofeedback group, individual sessions for 30 min, two times a week for 8 weeks (n = 50) vs control group (n = 29)	12 and 24 weeks	Mean difference in baseline scores at 24 weeks for fitness, biofeedback, and control groups, respectively (ANOVA between-group difference p values): VAS -5.5, -0.6, 1.3 (p=0.3), Tender points -0.6, -1.4, -1.9 (p=0.4), total myalgia score 12.8, 15.5, 25.3 (p=0.6)	"Thus compared to usual care, the fitness training (i.e., low impact) and biofeedback training had no clear beneficial effects on objective or subjective patient outcomes in patients with FM."	Data suggest comparable (in)efficacy between groups as neither fitness training nor biofeedback improved fibromyalgia symptoms better than controls.
Mehling 2005 (4.5)	Biodfeedback	RCT	Sponsored by the Mount Zion Health Fund, and Health Resources and Services Administration	N=36, patients with chronic low back pain.	Group 1: mean age 49.7±12.1; 5 males. Group 2: mean age 48.7±12.5; 5 males.	Group 1, 6 to 8 weeks (12 sessions) of breath therapy (n=16) vs. Group 2, 6 to	Baseline, 6 weeks, and 6 months.	Group 1 vs group 2, pre-6 week pain VAS score (Mean±SD): -2.71±2.23 vs -2.43±2.05 (p=0.74). Group 1 vs group 2, pre-6 week SF-	"In summary, this is the first study providing evidence that patients suffering from chronic low	Possible randomization failure as baseline data worse baseline differences in one group.

			fellowship of the US department of Health and Human Services. No mention of COI.			8 weeks (12 sessions) of Physical therapy. (n=12)		36 score (Mean±SD): +14.9±1.5 vs +21.0±2.5 (p=0.45). Group 1 vs group 2, relapse of low back pain at 6 months: 5/15 (33%) vs 1/11 (9.1%).	back pain can clinically improve with breath therapy. Changes in standard self-reported low back pain measures of pain and disability appear to be comparable to changes measured following high-quality, extended physical therapy."	
Altmaier, 1992 (score = 4.5)	Biofeedback	RCT	Industry sponsorship (National Institute for Handicapped Research) and no mentioned COI.	N = 47 consecutively admitted over 18-month period to low back rehab program	Mean age: 39.91; 33 males, 12 females.	Treatment programs: 1) standard inpatient rehab for chronic LBP (education QD and physical reconditioning, 2x/day PT, QD aerobic training, vocational rehab, n = 21); 2) Psychologically based program added to above	6 months	RTW not significantly lower in psychological group (47.6% vs. 67%). Patients improved in overall functioning at discharge and follow-up, but not different by group assignment.	"[T]he psychological treatment failed to add to the effectiveness obtained by the standard rehabilitation program."	Study suggests no additional benefit from relaxation training and coping skills when added to education, support, and exercise programs for chronic LBP.

						(operant conditioning, relaxation, biofeedback, charting of exercise behaviors, contingent verbal praise, chart on patient room wall, group and individual cognitive-behavioral coping training, n = 24). Follow-up at 3 weeks, 6 months.				
Frih, 2009 (score = 4.5)	4.5	RCT	No mention of industry sponsorship or COI.	N = 107 with symptomatic LBP, sciatica, and psychiatric disorders, and or behavior precluding participation in group therapy.	Mean age: Group A 34.7, Group B 36.9; 27 males, 80 females.	Group A (GpA): Group performs home-based rehabilitation program (n = 54) vs. Group B (GpB): Group received a standard rehabilitation program (n = 53).	3, 6, and 12 months	Significant difference for pain intensity in favor of GpA. VAS pain for GpA 25.1±20.3 and p<0.001, and GpB - 13.9±17.3 and p < 0.001. A total difference of, p = 0.003.	"The results of the present study suggest that a home-based rehabilitation program including exercises that match each individual patient's clinical profile can reduce chronic pain intensity and perceived disability, improve functional	Both groups improved over time, and most measures were not significantly different between groups, except VSA (ps=0.003) and Schirado (p<0.008).

									capacity and limit the psychological impact of LBP. However, this type of program requires high levels of motivation and regular supervision and patient evaluation."	
Glombiewski, 2010 (Score = 4.0)	Cognitive Behavioral Therapy	RCT	Supported by a doctoral thesis scholarship from the University of Marburg. No mention of COI.	N = 128 with chronic back pain.	Mean age 48.8 (11.7): 39 males and 77 females.	Cognitive–behavioral therapy (CBT) group (N = 35) vs Cognitive-behavioral therapy including biofeedback tools (CBT-B) group (N = 31) vs Wait-list control (WLC) group (N = 51).	6-months	CBT-B and CBT equally effective for pain intensity (using, Pain Intensity Questionnaire or PIQ): CBT-B, μ = 0.66 (95% CI 0.39–0.95) vs CBT, μ = 0.60 (95% CI 0.33–0.87)). CBT+CBT-B, 33.85% sig. improved vs WLC 13.73%. Primary outcome PIQ / Secondary outcome Pain Diary & RLS Scale & CS Scale & Doctor Visits; F (1.57, 177.98) = 3.45, p = 0.043 / (F (1.9, 133.32) = 1.29, p = 0.28, & F (1.96, 221.12) = 58.73, p < 0.001, & F (1.66,	"[B]iofeedback ingredients did not lead to improved outcome of a psychological intervention."	Waitlist control bias. Data suggest CBT intervention decreased chronic back pain and addition of biofeedback to CBT did not improve clinical outcomes. Not all patients randomized. Not blinded. Pooled CBT arms compared to control had improvements in many subjective measures but clinical significance

								186.64) = 8.8, p < 0.001).		uncertain. Data suggest no benefit to CBT when biofeedback is added.
De Sousa, 2009 (score=4.0)	Biofeedback	RCT	No mention of sponsorship or COI.	N = 60 patients with low back pain.	Mean age: 46.39 years; 17 males, 43 females.	Treatment group received 16 sessions using biofeedback (visual biofeedback F 1000 system) of muscular relaxation, techniques for cognitive restructuring, and abdominal strengthening exercises for eight weeks (N = 30) vs waitlist control group (N = 30).	Follow-up at baseline and 8 weeks.	No sig. results between treatment and control group in primary outcomes of VAS (p=0.131), Schober index (p=0.184), Roland-Morris Questionnaire (p=0.183), State-Trait Anxiety Inventory (State: p=0.071, Trait: p=0.425), Beck's Depression Inventory (p=0.647), or paraspinal and abdominal muscle electromagnetic levels (p=0.503 - 0.055).	"[O]ur treatment program did not lessen pain, improve quality of life or anxiety in patients with CLBP, or change paraspinal muscle toning during abdominal contraction. May be the biofeedback program is only valuable in a context of a cognitive-behavioral therapy."	Waitlist control bias. Data suggest lack of efficacy for primary treatment outcomes when compared to control.
Hallman 2011 (4.0)	Biofeedback	RCT	No mention of sponsorship or COI.	N=24 patients who sustained stress related chronic neck pain.	Mean age 40.5; 2 men.	Group 1: patients received heart rate variability biofeedback training for 10 weeks. (N=24) vs. Group 2: patients only received	Baseline and 10th session.	Group 1, baseline vs post-test for Short form 36 health survey "bodily pain" / Vitality / Social Function (mean±SD): 46.5±21 vs 71.8±18 (p=0.049) / 37.1±22 vs 57.5±22 (p=0.005) / 76.0±23.0 vs	"The present pilot study showed improvement in perceived health over 10 weeks intervention with HRV-biofeedback in subjects with stress-related	Pilot study with small sample. Data suggest slight trend in perceived health improvement in biofeedback group.

						breathing protocol at session 1 and 10 (n=10)		90.6±12 (p=0.047). above stats tested with ANOVA groupXtme with control group as well and stayed significant.	chronic neck-shoulder pain. Increased resting HRV as well as enhanced reactivity to HGT and CPT might reflect beneficial effects on ANS regulation, and may further suggest that this intervention protocol is suitable for a larger controlled trial."	
Bush, 1985 (score = 4.0)	Biofeedback	RCT	Industry sponsorship (MRC Studentship and a Gouvernment du Quebec FCAC Bourse Scholaire) and no mentioned COI.	N = 72 with chronic LBP	No mean age given. Age range 20-65; 38 males, 34 females.	Paraspinal EMG for ≥8 sessions (n = 23) vs. placebo (n = 24) vs. waiting list control (n = 25). Monitored self pain for 4 weeks. Assessments post-treatment and 3 months.	3 months	All groups with small but significant decreases in pain, depression and anxiety.	"[P]araspinal EMG biofeedback is not a specific treatment for chronic low back pain in a nonhospitalized population."	Correlation found at pre-treatment, but not present at post-treatment and follow-up.
Donaldson, 1994 (score = 4.0)	4.0	RCT	No mention of industry	N = 36 with chronic LBP	Mean age 38.0 years;	Single motor unit biofeedback	90 days, 4 years	McGill pain questionnaire average pain	"The EMG results showed	Baseline trends favored

			sponsorship or COI.		17 males, 21 females.	training (SMUBT, n = 11) vs. Relaxation training (n = 8) vs. educational program (n = 7). All groups received 10 sessions. Final follow-up at 4 years.		measure score (SD) biofeedback for pre/post/follow-up: 28.75 (15.11)/16.08 (14.98)/15.33 (15.66), p <0.05; for relaxation: 31.08 (12.39)/27.67 (12.63)/32.33 (11.31), p <0.05; for education: 34.50 (14.43)/28.58 (16.07)/20.08 (20.28), p <0.05. No significant differences for global VAS.	decreased amplitude and bilateral differences for the SMUBT and education groups. A 4-year follow-up revealed the SMUBT group remained symptom free."	biofeedback group as they are somewhat less severely affected. Data suggest biofeedback effective.
Asfour, 1990 (score = 4.0)	4.0	RCT	No mention of industry sponsorship or COI.	N = 30 with chronic LBP	Mean age: control group 46.53, experimental group 43.27; 13 males, 17 females.	EMG biofeedback as add-on therapy to exercise in increasing strength of trunk extensors (n = 15) vs. control (n = 15). Intervention administered 2 weeks of 4 week study.	2 weeks at post-intervention	Mean increase in strength (SD) for control vs. experimental group at final assessment: 284.22 (141.82) vs. 224.86 (209.19), p <0.01.	"[T]he proposed methodology was an effective tool to achieve a significant improvement in the strength of lumbar paraspinal muscles of chronic low-back pain patients."	Many details sparse. Data suggest biofeedback effective.

Appendix 1. Psychological and Biopsychosocial Assessment Tools

A Glossary of Psychological and Biopsychosocial Assessment Tools and Concepts Commonly Used for the Assessment of Patients in Rehabilitation*

Introduction

Pain-related disability is an exemplary biopsychosocial condition, with psychological and psychosocial concerns occurring concurrently with physical concerns. [19, 1053, 1054] To assess this condition, health professionals working in both research and clinical settings frequently gather data via a variety of biopsychosocial questionnaires and related assessment methods. The questionnaires used may be developed using a variety of methods, and can be employed as a systematic means of assessing a patient's pain, physical symptoms, functioning, quality of life, satisfaction with care, cognitions, mood, behaviors, and history – essentially any information that the patient can report, and may reveal important information about risk factors, diagnoses, or treatment outcomes. The potential value of these questionnaires was exemplified in a systematic review of the research on psychological test, suggesting validity and reliability that is comparable to that of medical tests. [886] These assessments are important, because if biopsychosocial complications go unrecognized and are not addressed, they may interfere with treatment outcome.

The goal of this appendix is to provide information that will promote the understanding of the use of biopsychosocial questionnaires. The tests listed here include both ones commonly used for screening, to assess outcomes in clinical settings or randomized controlled trials, as well as ones that are used in psychological evaluations. The test descriptions are provided for informational purposes.

Types of biopsychosocial assessment measures

Biopsychosocial assessment measures can be divided into three broad categories: screening, outcome assessment, and psychological evaluation. Measures intended for each of these uses tend to have certain characteristics, and awareness of these differences is beneficial when selecting a measure for a particular use. These three categores of measures can be described as follows:

1. **Screening measure.** A screening measure is a succinct instrument, sometimes as short as one or two questions. It is intended for administration to either an entire population, or an entire cohort of patients with a given condition. The frequency of utilization is typically in the initial exam and/or once a year. The objective of most screening measures is optimization of sensitivity, but not specificity. As a result, screening measures are able to identify at-risk populations, but as they are not able to suggest a diagnosis, a positive screening score is an indication for further diagnostic assessment. Screening measures are often administered by persons with minimal training, and the results are determined by a cutoff score (see Table 16).

2. **Outcome measures.** Outcome measures are unique in that they are intended to assess aspects of a patient's condition that are matters of concern, and that could potentially be changed by treatment. To accomplish this, an effective outcome measure should contain only changeable "state" items, as opposed to items assessing unchanging aspects of the condition. For example, if an outcome measure was intended to assess a patient's response to treatment for pain, a "state" item such as "My pain is so bad that I spend most of the day laying down" assesses a symptom that could be changed by effective treatment. In contrast, an unchanging item such as "I have had back pain for years" is a defining indication of chronic pain. However, this item is a historical fact and not something that any treatment could change. An outcome measure's power to detect change is a function of the degree to which it assesses relevant and changeable aspects of the patient's condition. An outcome measure is scored using an ipsative method which compares the patient to him/herself (e.g. "Is your score today better or worse than when you started?") (see Table 16).
3. **Psychological tests.** Psychological tests are part of the standard for the biopsychosocial assessment of chronic pain, and are generally indicated by either a positive psychological screening test or by clinical indications. The majority of psychological tests intended for clinical assessment utilize multidimensional assessment, and also have one or more validity measures that assess any tendency to magnify, minimize or otherwise distort symptom reports. Because of this, psychological tests are generally much longer than a typical screening test or outcome measure. These measures can be divided into multiple subcategories (see Table 16).
    - **Standardized vs. nonstandardized tests:** The majority of psychological tests intended for clinical assessment are "standardized" (see below) which allows test results to be compared to norms to produce a percentile rank. Most of these measures have scientific peer reviews that are published by the Buros Institute, and are protected by test security (e.g. not posted on the internet, and requiring a credentials check to obtain) which reduces the risk that they can be manipulated. These are interpreted by a psychologist and/or physician with appropriate training. In contrast, some nonstandardized psychological measures are freely available (e.g., The Pain Catastrophizing Scale, the CES-D, PROMIS measures, the Pain Anxiety Symptom Scale, the Pain Self Efficacy Scale) and scoring keys for the scales are freely found. These measures are commonly used in research settings. In contrast to the tests above, while these measures offer a brief assessment of a specific dimension, they are generally not standardized, lack validity measures, and do not offer a comprehensive overview of biopsychosocial risk factors. These latter measures require less expertise to administer and interpret than standardized multidimensional tests.
    - **Psychological vs. Biopsychosocial vs. Neuropsychological tests:** Psychological tests may also be subdivided by the domain to be assessed. The traditional division between these tests was that of psychological measures that assessed factors related to mental health diagnoses (e.g., mood, personality, psychosis, addiction), and neuropsychological measures that assess brain functioning (e.g., memory, ability to learn, knowledge). More recently, biopsychosocial measures have been developed to assess not only psychological variables, but also assess a patient's biological symptom complaints, perception of and beliefs about a medical condition, how a patient copes with a medical condition, any psychological reaction to a medical condition, and social support or secondary gain that could influence the outcome of medical treatment.

The comprehensive assessment of the patient with chronic pain most commonly involves a biopsychosocial assessment. The biopsychosocial evaluation of the patient focuses on interpreting the

patient's physical symptoms and complaints within a psychosocial context. A biopsychosocial evaluation may consist of a clinical interview alone. However, the standard for the assessment of chronic pain includes the use of standardized psychological testing. Psychological tests are used for a variety of purposes, including measurement or description of patient traits, diagnosis, tracking change with treatment, and attempting to predict treatment outcome. While pain and disability are widely regarded as being biopsychosocial phenomena, the interrelationships between pain, functioning, physical symptoms, psychological, social and other diagnostic and outcome variables in patients with chronic pain is complex. Professionals utilizing these assessment instruments should be familiar with the strengths and limitations of the chosen assessment method.

Definitions

Cutoff score: A test score used to determine what is a low, average, high, or very high score. Cutoff scores may be determined by data or by reference to diagnostic criteria, or they may be arbitrary.

Ipsative assessment: Comparing a patient's current status to his or her past status (e.g., patient reports being able to function better than before). This is often done in treatment research, and is a well-established method of looking at changes in group scores.

Normative assessment: Comparing a patient to a reference group called a "norm group" (e.g., patient reports more difficulties with functioning than 92% of patients in rehabilitation). Normative scores allow a determination that a particular patient has a high or low score. Any scale capable of normative assessment can also perform ipsative assessment. The most common means of normative assessment used by psychological tests is the T-score.

Norm Group: A reference group to which a patient's score is compared. A general rule of thumb for norm groups used by psychological tests can be stated metaphorically in the following manner: If you are judging apples, comparing apples to apples is better than comparing apples to oranges. The closer the norm group is to the patient's status and situation, the more relevant the resulting score.

Reliability: The ability of a test or scale to produce consistent results, e.g., if a test is given twice in a short time frame, the results should be very similar.

Standardized Test: A standardized test has the following characteristics:

- Standard test administration materials
- Manual/user guide containing
    - Documentation of purpose and uses of test
    - Documentation of test norms and norm groups
    - Instructions for calculating standardized scores (which compares the patient's score to the norm group)
    - Method for interpreting standardized scores
    - Documentation of test reliability and validity
    - Documentation of test development process

T-score: The most commonly used standardized score on psychological tests. A t-score has a mean of 50 and a standard deviation of 10.

Validity: The extent to which a test or scale actually measures what it purports to measure. A common validity concern when psychological tests are used to assess medical patients is that many of these tests use both psychological and medical symptoms to diagnosed psychiatric disorders, and this can lead to false positive findings. For example, if a test of depression includes items about weight change, sleep disturbance, and loss of libido, to what extent is it actually measuring the effects of pain, inactivity, or medication side effects as opposed to depression?

Validity measure: A measure on a test that attempts to assess whether a subject's responses are valid as opposed to being the product of illiteracy, random responding, oppositional behavior, faking, or other attempts to manipulate the results of the test.

Testing Concepts

Standards for Psychological Test Use

Biopsychosocial tests vary greatly with regard to what they are intended to assess and the degree to which they have met accepted testing standards. There are a multitude of clinical and forensic standards that pertain to the assessment of the patient with chronic pain [1439]. There are also clearly defined standards for psychological tests, and term "standardized psychological test" indicates that it is a measure whose development sought to meet the criteria defined by a work called the *Standards for Educational and Psychological Testing*.(2014) The *Standards* are endorsed by the American Psychological Association and numerous other governmental, professional, credentialing, educational, and advocacy bodies.(1055) These standards provide specific guidelines regarding standardized tests, including test development, validity, reliability, norms, fairness issues, the appropriate use of testing, and documentation. A standardized test is evaluated and normed on a population sample, with the norm group ideally being composed of a sample accurately representing the population with regard to age, gender, education, socioeconomic status, racial groups, region, and medical condition. When a test has undergone a formal validation process as specified by *The Standards*, the results of this process are documented in a manual. Most standardized psychological tests are submitted to the Buros Institute for peer review and these reviews are published in the *Mental Measurements Yearbook*.

The *Standards* state that in order for a psychological test to effectively identify unusual levels of a symptom or trait in an individual, the test should be standardized. A standardized test has a standard set of questions and a standard method of administration, scoring, and test interpretation. The resulting raw score is generally converted to standardized scores, which are usually based on a comparison to one or more "norm" groups. These standards also make it clear that the test administrator must have training in test administration and interpretation in order to make meaningful and accurate conclusions. Moreover, the *Standards* also indicate that the standardized tests must be administered and interpreted in a similar method by any clinician who utilizes the tests. While this may seem self-evident, conducting standardized testing in a manner differently from the standard method, places doubt on the resulting test data and how it may be utilized in the evaluation, diagnosis, and treatment process. Overall, any psychological test is preferred to the extent that it is standardized.

Ipsative and Normative Assessment

Ipsative assessment is the simplest method of assessment and can be utilized to compare the individual's performance scores in a pre-post manner. Ipsative assessments are common in medicine and are illustrated by the following examples:

- Prior to treatment, patient could walk for 15 minutes on a treadmill, but after 4 weeks this increased to 30 minutes.
- Prior to treatment, patient endorsed 12 of 20 items on a depression checklist, but after 8 weeks of treatment endorsed only 6.
- Prior to treatment, patient reported a pain level of 6, but after a trial of NSAIDs pain reports decreased to 3.

Ipsative measures compare a patient's present scores to the patient's own previous scores. These types of comparisons allow the assessment of change by a patient, but do not indicate if a patient's scores are high or low. Ipsative measures of this type can be very effective in research, but since this method cannot identify high or low scores, it has limited applicability in clinical assessment.

In contrast to ipsative assessment, some psychological tests employ cutoff scores. To employ this approach, a patient's score is compared to cutoff levels that determine what is interpreted as a low, average, high, or very high score. Cutoff scores may be determined by data or by reference to diagnostic criteria, or they may be arbitrary.

In psychological assessment, the preferred method of assessment is called normative assessment. Normative assessment compares the patient's score on particular measure to a reference called a "norm group," whose average score is called the "norm." Through the use of norms, standardized scores can be calculated. Through this process, it becomes possible to make more precise statements about individual patients. In this manner, standardized tests scores provide a means of identifying whether a patient's symptomatic complaints are unusually high or low relative to the norm group. Normative assessments can also be used in an ipsative manner by comparing the patient both to a group and to his or her own prior performance. Overall, normative assessment provides more information than ipsative assessment, and the use of norms is one of the standards for clinical assessment advocated by the *Standards for Educational and Psychological Testing*.

The nature of the norm group is extremely important. Consider the difference that the three norm groups below make on the follow statement:

This patient in physical rehabilitation is reporting more difficulties with functioning than 92% of…

- healthy persons in the community
- patients in physical rehabilitation
- patients with asthma
- patients with schizophrenia

If the patient is undergoing assessment as part of a physical rehabilitation program, the comparison of the patient's score to healthy persons in the community indicates that the patient is reporting more problems with functioning than the average healthy person. In contrast, using other patients in rehabilitation as the norm group is probably more useful, as if this patients score was higher than that of 92% of other patients, then this is a patient with unusually severe complaints. Alternately, the meaning of the third and fourth comparisons make less sense.

The *Standards* also state that during the development of a test, due consideration should be given to matters of diversity. Consequently, the nature of a test's norms is especially important. If a test's norm group is not sufficiently diverse, the test results could be biased. On the whole, tests which use standardized scores based on norms are preferred. Further, the more relevant the norms are to the patient's medical, gender, race/ethnicity, age, and educational and other group status, the more meaningful the resultant score.

Validity, Reliability and Standardization

For a psychological test to be used in the clinical setting, three characteristics that need to be considered are the reliability, validity, and standardization of that test. Test reliability can be determined by a relatively straightforward process. Internal reliability refers to the degree to which the items on a scale are internally consistent with each other, as opposed to being prone to contradictory findings. Test-rest reliability or test stability refers to the degree to which two administrations of the same test produce the same results. A determination of reliability is an integral part of the development of a standardized test.

The phrase "Text X is a validated measure" is sometimes heard, but this phrase misrepresents and oversimplifies the concept of test validity. It is not correct to say that a test is valid, rather it should be stated that there is a certain level of evidence that a given test is valid for a particular purpose. Test validity is more complex, and can be conceptualized as consisting of three levels.

The first level of test validity is based on the nature of the diagnosis or condition that is being assessed. If a psychological or medical condition is known to have a certain number of symptoms, then it is generally preferable to have items assessing those symptoms. This level of validity, called content validity, may be determined by clinical judgment, or by a panel of experts. A second level of validity pertains to the degree to which a scale actually measures what it is supposed to measure. Thus, if a scale is a measure of depression, it should exhibit a positive correlation to other scales measuring depression, or to clinical judgments of depression. In general, most standardized tests have met these two levels of validity. However, as there are multiple forms of depression, such as major depression, bipolar depression, dysthymia, and adjustment disorder with depression, a test may be designed to sample only certain aspects of depression. Consequently, while the results of various measures of depression sometimes disagree, this may be understandable if the nature of each instrument is understood.

The third level of validity has to do with the ability of the test to predict current or future diagnoses, traits, behaviors or medical outcomes. Depending on the measure, there may be a greater or lesser amount of evidence to support a particular clinical use. There is a promising and increasing body of

evidence suggesting predictive abilities of standardized psychological tests, e.g., to predict the relative outcomes of surgery, multidisciplinary treatment, and other forms of medical treatment [1428] [1429-1432].

Beyond validity and reliability, the *Standards for Educational and Psychological Testing* set more stringent criteria for the assessment of individuals in the clinical setting. [1055] According to the *Standards*, in order for a psychological test to fairly assess individual patients, that test should be standardized. That means that in addition to evidence of reliability and validity, the test should have standardized test form/materials, instructions, scoring, norms, and interpretation, as this helps to reduce the error variance introduced by nonstandard assessment methods. All of this information and the test development process and evidence of validity and reliability should be documented in a test manual. Standardization makes it possible to scientifically determine if a particular patient's score is unusually high or low. In general, for clinical assessment, a standardized test is preferred.

Psychological Screening

Current preventive medicine policies recommend screening for a number of medical and psychological conditions. While medical screening is usually accomplished by examination or medical tests, psychological screening is usually accomplished by questionnaire. Under Federal healthcare regulations, the psychological conditions most commonly screened for are depression, substance abuse, and nicotine dependence.[6] With regard to patients with chronic pain, most opioid guidelines recommend psychological assessment of substance abuse vulnerability prior to long term opioid treatment.[7] Additionally, comprehensive chronic pain guidelines recommend screening patients with chronic pain for psychosocial contributions to pain,[8-10] and common psychological conditions to screen for also include anxiety, somatization, dysfunctional cognitive styles (e.g. catastrophizing), or perception of disability / low functionality.[11]

The American Psychological Association has noted that while the terms psychological screening and psychological assessment are sometimes used interchangably, it is important to distinguish between them.[12] The differences between psychological screening and assessment are summarized in Table 16.

Table 16. Differences between psychological screening and assessment

Psychological Screening	Psychological Assessment
Brief	Comprehensive
Part of a routine visit	Requires a dedicated visit
Designed for early detection of psychosocial complications and identify patients in need of psychological referral	Designed to integrate the results of multiple psychological measures with patient history, medical findings and clinical observations
Narrowly defined scope of assessment	Typically a multidimensional assessment
May be administered by clinicians, support staff with appropriate training, or self administered	Requires interpretation by a psychologist or physician with training in these assessments
Positive finding determined by cutoff score	Positive finding determined by standardized scores which typically produces a percentile rank

Positive finding indicates a need for further psychological assessment	Goal is to reach a definitive conclusions about diagnosis, make determinations about patient disposition, develop treatment plan, and respond to referral questions

Screening tests are designed in such a way as to be short and highly sensitive, at the cost of low specificity. For example, if we think of body temperature as a medical screen, a temperature of 101 F can suggest that something is wrong, without providing any specific information about diagnosis. Similarly, a positive depression screen suggests that the patient is reporting being distressed, without telling us if the patient has diagnosable depression, and if so, if the depression is due to an injury, a bad marriage or bipolar disorder. Consequently, like medical screens, the purpose of a psychological screen is not to provide a definitive diagnosis but rather to indicate a need for further assessment.

For the treating provider, brief psychological screening questionnaires may provide information that can help to identify patients with psychological conditions. When psychological screening assessments are positive, or when there are other indications of psychological dysfunction or uncorroborated medical symptoms, a comprehensive psychological evaluation is indicated.

Psychological and Biopsychosocial Outcome Measures

In contrast to screening measures that are intended to identify patients in need of further assessment and treatment, outcome measures are intended to assess the patient's response to treatment. Like screening measures, outcome measures are brief, and may be administered by clinicians, support staff with appropriate training, or self-administered. Outcome measures may be administered in three different ways: pre-post, serial, and post hoc (i.e., occurring after the treatment).

A pre-post assessment is an ipsative assessment method that compares a patient's baseline level of functioning at the start of treatment to their functioning when treatment has concluded. A pre-post assessment is required to determine the degree to which any treatment actually produced change, and plays a critical role in determining treatment efficacy. A strength of pre-post assessment is that by identifying patients with severe pre-treatment symptoms, even a moderate level of functionality post-treatment is an indication that the patient benefited greatly from treatment. This assessment method helps to control for severity of the medical condition, and can be useful for providers who treat patients with catastrophic injuries.

Serial assessment is an ipsative method similar to pre-post assessment, except that while pre-post assessment occurs at the beginning and end of treatment, serial assessment is ongoing and occurs at regular intervals (e.g., once a week, once a month, etc.). A potential use of serial assessment is that it can help to determine when a patient is not benefitting from treatment, and more broadly when *maximum medical improvement* occurs. Maximum medical improvement (MMI) is said to occur when a patient's progress in treatment plateaus, and where it is believed that the patient is unlikely to make gains from further treatment. One method to determine the endpoint of treatment is to use the serial assessment of a relevant functional measure, as the scores may be plotted and graphically illustrate when a treatment plateau occurs.

In theory, serial assessment is an excellent means of determining undertreatment (i.e., stopping treatment when scores are still improving) and over treatment (i.e., continuing to treat after the response to treatment has plateaued). In practice however, there are a number of major threats to the validity of serial assessment.

The first threat to the validity of serial assessment has to do with floor and ceiling effects. To understand the problem created by these effects, consider a hypothetical measure of functioning we will call The Weightlifting Test. Suppose The Weightlifting Test had the following items:

After performing your exercises in the gym, answer the following questions True or False:

1. I am able to lift 40 pounds.
2. I am able to lift 42 pounds.
3. I am able to lift 44 pounds.
4. I am able to lift 46 pounds.
5. I am able to lift 48 pounds.
6. I am able to lift 50 pounds.

This hypothetical Weightlifting Test will make fine discriminations in a patient's level of functioning from 40-50 pounds, and within that range would be a valid measure and reliable measure. But below the "floor" of 40, improvement in strength from 10 to 30 pounds will not register on this measure. Similarly, improvement in strength from 80 to 100 pounds will not register either, as that change is above the "ceiling" of the instrument. When changes are occurring below the floor or above the ceiling on an instrument, this measure is no longer valid, as it will wrongly appear that the patient's condition is not changing when that is actually not the case. Note that instruments constructed using Item Response Theory (e.g., PROMIS) usually have fewer problems with floor/ceiling effects, as this test development method excels at controlling this.

A second threat to the validity of our hypothetical test has to do another source of error called a content validity problem. To illustrate this problem, suppose a patient's Weightlifting Test score remained at a constant 46 pounds for four weeks. This would appear to suggest that the patient is no longer benefitting from that treatment. However, during this same period, while strength remained unchanged, the patient may have made gains in range of motion. The problem is that as the content of the items of The Weightlifting Test do not assess range of motion, The Weightlifting Test is not a valid measure of changes in range of motion. This is called a content validity problem, and when it occurs in this context a patient's progress may appear to plateau, when she/he is actually still progressing on a different dimension.

There are also other threats to the validity of serial assessment. These include that many treatments have a typical time required to produce an effect (e.g., after 30 minutes of exercise a patient may not be any stronger). Consequently, patients may initially exhibit a baseline plateau before the benefits of the treatment are seen, and this baseline plateau does not indicate termination of treatment. In other cases, patients may exhibit a treatment plateau not because they are at MMI, but because they are not

getting the treatment that they need. Overall, while serial assessments potentially have value in assessing response to treatment, there are numerous ways that it can produce erroneous results.

In contrast to pre-post and serial assessments, post hoc assessments are administered on one occasion after treatment has concluded. Post hoc measures most commonly assess matters such as patient satisfaction with care, but may also assess patient disposition following care, such as did the patient return to work? In some cases, post hoc measures attempt to simulate a pre-post assessment by utilizing patient recollection (e.g., "Do you think you are better now than when you started?"). However, as treatment may have begun months and sometimes years in the past, patient recollections of their own baseline level of functionality may not be reliable.

Finally, in some economic models, patient outcomes are used to incentivize providers (e.g., "pay for performance"). Alternately, whether or not a patient has responded positively to treatment at some point in time is sometimes used to make determinations regarding whether or not more treatment is indicated. Pre-post and post hoc outcome assessment methods often tap different aspects of medical treatment outcome, and a comprehensive outcome assessment protocol would include both.

The Psychological Evaluation Process

Due to the prevalence of psychological conditions observed in patients with chronic pain, it is important to psychologically assess the patient to ensure that these conditions are identified and addressed in the treatment process. However, clinical biases and an over-reliance on subjective perceptions from both the treating professional and patient can lead to inaccurate diagnosis and treatment failure. Objective psychological tests can be helpful in this regard, by providing a system of checks and balances for any biases in treating professional's clinical impressions. Thus, appropriate psychological tests provide a means to make the evaluation and treatment process more objective.

For the treating provider, brief psychological questionnaires can provide information that can help to identify patients with psychological conditions (see Table A4c). In conjunction with an interview and examination, these questionnaires can facilitate a comprehensive assessment of the patient. When these screening assessments are positive for emotional distress, or when there are other indications of psychological dysfunction or uncorroborated medical symptoms, a comprehensive psychological evaluation is indicated and they also reveal therapeutic targets and the likely need for brief educational interventions about pain.

When patients are referred for a psychological assessment, the referral should include a specific clinical rationale. Psychological assessment is distinct from neuropsychological assessment. Neuropsychological assessment relies primarily on measures of cognitive ability, memory and concentration to assess patients with brain injury or disease. In contrast, psychological assessment focuses on the assessment of personality, mood, psychosis, emotional trauma, social conflicts, and the patient's beliefs about and reports of pain and other somatic symptoms. In relatively straightforward cases, extensive psychological testing is not always needed. The clinical interview though provides a mechanism for screening those individuals who are a higher risk for psychological concerns (e.g., substance abuse, past psychological history, chronic physical concerns, not progressing as anticipated, or lack of objective medical evidence

that supports the individual's symptoms). When these risk factors are present, the patient is likely a candidate for standardized psychological testing.

The professional performing the psychological evaluation is generally a psychologist with PhD, PsyD, or EdD credentials, or in some states may be a mental health professional. A physician with MD/DO credentials and proper training may perform the initial comprehensive evaluation. These professionals should have experience in diagnosing and treating chronic pain disorders in injured workers. Screening and outcome measures are commonly administered by a variety of professions. In contrast, standardized psychological and neuropsychological tests are most commonly administered by psychologists with a PhD, PsyD, or EdD degree. Standardized psychological and neuropsychological tests can also by administered by physicians or mid-level professionals with appropriate training or supervision, but, for some tests, documentation of appropriate training is required to access standardized measures protected by test security.

When psychological assessments are conducted, generally at least two standardized psychological tests are required to assess the same concern. One psychological test may not measure all of the variables that need to be assessed, thus additional tests may be needed to address all of the referral concerns. In general, evaluations utilizing shorter, one-dimensional tests (those that measure only one psychological concern) require the use of a greater number of tests, while the reliance on larger, multi-dimensional tests tend to result in fewer tests being needed. That said, a general rule for psychological testing is to use the minimum number of tests necessary to adequately assess the identified concern or referral question(s). Additionally, psychological tests should not be given without consideration of the referral question(s) to be answered or psychological concern(s) that need to be ruled in or out. The use of additional psychological tests is not indicated if they do not objectively measure the identified clinical issue(s), are redundant measures of clinical concerns that have already been assessed or are not validated for clinical assessment. A systematic review found that the variables of pain, functioning, depression, anxiety, somatization, passive coping, job dissatisfaction, low education, and longer time off of work are associated with a poor outcome from lumbar surgery [1057]. Expert consenus has also identified a number of other less well researched variables [1440]. Presurgical psychological evaluations for lumbar surgery should assess these variables, in addition to a more general assessment of psychopathology.

The test descriptions are provided for informational purposes only in Tables A1–A3. These are not exhaustive lists, and are not intended to make recommendations. Additionally, this information is not intended to direct payers regarding which tests should be covered for diagnostic purposes. Furthermore, the information is not intended as a guiding document for legal concerns. Each area represents multiple complex issues that are governed by different state and federal regulations [1439]. The final decision about which tests to use must be left to the evaluator, and the science is not at a point where it can be stated that a specific test is preferable for any purpose. Within each section, tests are listed in alphabetical order.

If the psychological evaluation is being conducted in order to qualify the patient for a specific treatment protocol or surgery, the psychologist should not be employed by the organization or practice performing that service. An exception to this would be multidisciplinary programs, where the psychological

assessment and treatment are both part of an integrated program. Users should also be aware of the potential for test data to become forensic evidence either during or after the treatment process. While this appendix is not intended to provide professional direction regarding the complexities of the forensic process, the test user must understand that psychological test results as well as the test user's interpretation of the data have a significant potential for being introduced into the legal process with the chronic pain population. Consequently, it is important to recognize this potential when conducting the evaluation.

The release of personal health information in a psychological evaluation should be mindful of the HIPAA Minimum Necessary Standard. This standard states that the provider should exercise reasonable efforts not to disclose more than the minimum amount of information needed to accomplish an intended purpose. When the results of a psychological evaluation are being released to another provider for treatment purposes, this standard does not apply. However, in Worker Compensation settings, the results of a psychological assessment may be available to the employer, especially if the patient is in litigation. When this is the case, the Minimum Necessary Standard may apply to sensitive psychological information.

Identifying Invalid Test Protocols

Unlike research settings, information gathered from psychological tests in the clinical setting is not anonymous, but specific to the individual. This information serves an important role in making clinical decisions pertaining to treatment or disability awards. Because of this, the individual may be incentivized to bias the information provided. Consequently, clinical tests often include validity measures that assess any reporting biases on the part of the patient.

There are a variety of patient behaviors that could invalidate the results of a psychological test or other self-report measure. [1056] A patient may provide distorted or incorrect information for a variety of reasons, including secondary gain in the form of money, attention, access opioid or other medications, or work avoidance. Alternately, some patients may fail to answer out of concerns about the limits of confidentiality, embarrassment, confusion, or illiteracy. While some psychological tests are more subtle, others are totally transparent to the patient and the results can be manipulated with ease. To control for this, many psychological tests employ validity indices. Validity indices generally fall into one of five categories: 1) validity measures designed to detecting exaggerating, "simulation" or "faking bad"; 2) validity measures designed to detecting minimizing, "dissimulation" or "faking good"; 3) validity measures designed to detect random, inconsistent, or bizarre responding; and 5) validity assessment that tests for contradictory responses. A further consideration that can sometimes invalidate a test is a failure to respond (leaving items blank), which can suggest either a lack of motivation, difficulty with comprehension, fatigue, or a resistance to answering certain questions.

Psychological screens and outcome measures as a rule do not have validity measures. In contrast, psychological assessments usually include validity measures. When validity indices are absent, the test administrator may not be able to determine if the test taker is minimizing, exaggerating, or otherwise distorting responses. When there are strong incentives for the patient to manipulate the test responses, such as financial gain, access to opioid prescriptions, access to other desired treatments, or work

avoidance, transparent assessment protocols without validity measures should be avoided. Overall, the use of standardized psychological tests that incorporate measures to assess the validity of patient responses is strongly suggested when performing psychological assessments, as an important part of a psychological assessment is determining any biases that might influence how a patient presents information. It should be noted that psychological test results should always be used in combination with an interview, medical records and other sources of information when evaluating a patient.

What Psychosocial Variables Need to Be Assessed?

As noted in the section on Psychological Evaluation in the Chronic Pain Guideline introductory text, there are a number of reasons why a patient may be referred for psychological assessment. While some concerns, such as depression and anxiety, are commonly assessed, more specific concerns to be assessed are determined by the nature of the referral. When psychological tests are used, the clinician (usually a psychologist) is responsible for the selection and use of appropriate test instruments that adequately and objectively assess noted clinical concerns [63][12].

Several psychosocial variables have been identified as predicting surgical outcomes (see Table A1). [1057][1428, 1430, 1433-1436] The evaluation of these variables is indicated when performing presurgical psychological evaluations prior to lumbar surgery. The Den Boer and Celestin studies concluded that the outcome of lumbar surgery was determined by a set of multiple biopsychosocial variables – pain, functioning, depression, anxiety, somatization, passive coping, job dissatisfaction, low education, and longer time of work – suggesting that when more of these factors are present, the worse the prognosis or surgical outcome.

Table A1. Glossary of Psychological Screening Measures for Depression and Anxiety		
Assessment Task	**Test**	**Description**
Screening Tools for Depression or Anxiety	***These brief tools are intended for the assessment of depression and anxiety and can be used by the provider to screen for affective distress. They should not be used for diagnostic purpose.***	
	BDI II **5-10 minutes**	**Beck Depression Inventory II*** http://www.pearsonclinical.com/psychology/products/100000159/beck-depression-inventoryii-bdi-ii.html *Measures:* Assesses depression using items incorporating a broad range of cognitive, affective and physical depressive symptoms *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores; widely used clinically and in research *Comments:* Has scoring software. Scale includes physical symptoms that could be attributable to depression, illness, or medication adverse effects.(1058-1062) The BDI for Primary Care (BDI-PC) is a shorter version of the BDI II and considered to be independent of physical function. [1063] It produces only a yes/no indication for depression. A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
	CES-D **3-5 minutes**	**Center for Epidemiological Studies Depression Scale** http://cesd-r.com/ *Measures:* Depression *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores *Comments:* Not copyrighted, freely available, has been widely used in research. A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
	HDI **3-5 minutes**	**Hamilton Depression Inventory** https://www.tjta.com/products/TST_020.htm *Measures:* A brief measure self-report inventory that assesses depressive symptomatology. *Validity measures:* None *Norms and Validation:* Uses community norms *Comments:* Has scoring software A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.

	HDS or HAM-D **3-5 minutes**	**Hamilton Rating Scale for Depression** http://healthnet.umassmed.edu/mhealth/HAMD.pdf *Measures:* A brief rating scale filled out by the professional that assesses a broad range of cognitive, affective, and physical depressive symptoms *Validity measures:* None *Norms and Validation:* Uses cutoff scores *Comments:* Since the professional fills out this measure, results may be affected by interviewer bias. A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
	STAI-AD **10 minutes**	**State-Trait Anxiety Inventory for Adults** http://www.mindgarden.com/145-state-trait-anxiety-inventory-for-adults Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press. *Measures:* Assess both anxious states and anxious tendencies without reliance on physical symptoms *Validity measures:* None *Norms and Validation:* Community norms, with male and female subgroup norms by age group. *Comments:* Used in a considerable amount of research. A positive screen for anxiety indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing. This screen distinguishes anxiety from depression. It is available in multiple languages.
	Zung Depression Scale **3-5 minutes**	**Zung Depression Scale** http://healthnet.umassmed.edu/mhealth/ZungSelfRatedDepressionScale.pdf *Measures:* A brief measure of depression that assesses a broad range of cognitive, affective, and physical depressive symptoms *Validity measures:* None *Norms and Validation:* No norms used, only estimated cutoffs whose applicability to medical patients is uncertain. *Comments:* Widely used in research. Scale includes physical symptoms that could be attributable to depression, illness, or medication side effects. Not copyrighted, freely available. A positive screen for depression indicates that the person should be referred to a clinical psychological for additional evaluation and potential psychological testing. A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.

[*] *Proprietary.*

Table A2. Glossary of Psychological Screen Measures for Assessing Pain and Function		
Assessment Task	**Test**	**Description**
Brief Functional Assessment Tools	***These brief tools are intended for the assessment of functioning, and can be used to track progress in treatment. These tools should not be used for diagnostic purposes.***	
	Oswestry **4-6 minutes**	**Oswestry Low Back Pain Disability Questionnaire** Fairbank JCT & Pynsent, PB (2000) The Oswestry Disability Index. *Spine*, 25(22):2940-2953. *Measures:* Problems with functioning *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores *Comments:* Intended for assessing disability secondary to back pain and injury. This commonly used measure of functioning in research studies is known to be sensitive to assessing change. Original version has been shown to be an effective research outcome measure, but there are also several modified versions. Cutoff scores derived for original Oswestry should not be applied to modified versions. Not copyrighted, freely available. A positive screen indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
	PDQ **3-4 minutes**	**Pain Disability Questionnaire** http://www.integrativepainsolutions.net/Pain_Disability_Questionnaire.pdf *Measures:* Assesses disability associated with pain *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores *Comments:* Brief tool that appears to be a very sensitive measure of disability associated with pain. [1072] One study found that it predicted rehabilitation outcome. [1073] Not copyrighted, freely available. A positive screen indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
	POP **3-5 minutes**	**Pain Outcomes Profile** http://www.aapainmanage.org/resources/tools/pain-outcomes-profile/ *Measures:* Assesses pain and pain interference with a variety of activities *Validity measures:* None *Norms and Validation:* Cutoff scores. Norms have not been released at time of publication. A positive screen indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.

	Roland and Morris Disability Questionnaire **3-4 minutes**	**Roland and Morris Disability Questionnaire** http://www.rmdq.org/ *Measures:* Problems with functioning *Validity measures:* None *Norms and Validation:* No norms, uses cutoff scores *Comments:* Intended for assessing disability secondary to back pain and injury. Commonly used measure of functioning in research studies. Not copyrighted, freely available. *Languages:* English and Arabic, Chinese, Croatian, Czech, Danish, Dutch, Flemish, French, German, Greek, Hindi, Hungarian, Iranian, Italian, Japanese, Kannada, Korean, Marathi, Norwegian, Polish, Portuguese, Romanian, Russian, Spanish, Swedish, Tamil, Telugu, Thai, Tunisian, Turkish, and Urdu. A positive screen indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.
Brief Pain Assessment	***These brief screening measures are intended for pain assessment and can be used by the provider to track changes in pain, but should not be used for diagnostic purposes.***	
	BPI–Long Form **15-25 minutes**	**Brief Pain Inventory – Long Form** http://www.npcrc.org/files/news/briefpain_long.pdf *Measures:* Assesses pain, pain variation, pain distribution, and degree to which pain interferes with functioning. Also includes a variety of questions about pain quality, response to treatment, and open-ended questions to which the patient can respond. *Validity measures:* None. *Norms and Validation:* No norms or cutoff scores. *Comments:* Only assesses problems with functioning associated with pain as opposed to physical limitations.
	Brief Pain Inventory – Short Form **4-6 minutes**	**Brief Pain Inventory – Short Form** http://www.npcrc.org/files/news/briefpain_short.pdf *Measures:* Assesses pain, pain variation, and pain distribution through drawing. Also assesses degree to which pain interferes with functioning. *Validity measures:* None. *Norms and Validation:* No norms or cutoff scores. *Comments:* Only assesses problems with functioning associated with pain as opposed to physical limitations. A positive screen for depression indicates that the person should be referred to a clinical psychologist for additional evaluation and potential psychological testing.

	MPQ **Short Form** **3-5 minutes**	**McGill Pain Questionnaire** http://prc.coh.org/pdf/McGill%20Pain%20Questionnaire.pdf *Measures:* Assesses sensory, affective, and evaluative dimensions through the use of verbal descriptors of pain experience as opposed to pure pain intensity. *Validity measures:* None. *Norms and Validation:* Cutoff scores. *Comments:* Some debate over what the scale is actually measuring; may not be useful for tracking changes in pain intensity due to treatment. *Languages:* English and Amharic (Ethiopian), Arabic, Chinese, Czech, Danish, Dutch, Finnish, Flemish, French, German, Greek, Hungarian, Italian, Japanese, Norwegian, Polish, Portuguese, Slovak, Spanish, and Swedish.
	NRS **< 1 minute**	**Pain Numerical Rating Scale** http://www.rehabmeasures.org/PDF%20Library/Numeric%20Pain%20Rating%20Scale%20Instructions.pdf *Measures:* Pain intensity. *Validity checks:* None. *Norms and Validation:* No norms or cutoffs; used in thousands of research studies. *Comments:* Recommended by JCAHO. Extremely easy to use, most often administered verbally. Proven usefulness in ipsative assessment, but has not been normed. Complete lack of standardization with literally thousands of variations. No defined instructions with regard to what constitutes a 10 (e.g., worst pain imaginable), time frame (e.g., pain now vs. pain last week), location (overall pain vs. pain in one body site), scaling (e.g., 1-10, 0-10, 1-100). Verbal rating may not be presented the same way each time.
	VAS **<1 minute**	**Pain Visual Analog Scale** https://www.painedu.org/downloads/nipc/pain%20assessment%20scales.pdf D. Gould et al. Visual Analogue Scale (VAS). *Journal of Clinical Nursing* 2001; 10:697-706 *Measures:* Pain intensity. *Validity checks:* None. *Norms and Validation:* No norms or cutoffs; used in thousands of research studies. *Comments:* Proven usefulness in ipsative assessment, but has not been normed. Complete lack of standardization with literally thousands of variations. No defined instructions with regard to what constitutes the highest pain level, time frame, location, and visual presentation (e.g., are numbers listed, line length, horizontal or vertical line). More difficult for some people to use than numerical scales. May be more sensitive to small changes in pain than numerical scales. Used extensively in research. Given that it must be administered in a printed form, is more likely to be presented the same way each time than a verbal Numerical Rating Scale.

	Quebec Back Pain Disability Questionnaire **5 minutes**	**Quebec Back Pain Disability Questionnaire** http://scale-library.com/pdf/Quebec_Back_Pain_Disability_Scale.pdf *Measures*: 20 daily activities that are categorized into 6 types of activities. These activities are bed/rest, sitting/standing, ambulation, movement, bending/stooping, and handling of large/heavy objects. This measure is for low back pain and limitations in functioning. This is a self-administered screen. *Validity*: Construct, Convergent, Content and Face *Scores*: Broken into 5 groups: mild, moderate, severe, very severe, and extreme perceived disability. Movement from a higher group to a lower group suggests improvement. Mild and Moderate Scores are considered Group A= likely to be fully back to work within 1 year with the same employer. All remaining groups are Group B. Group B patients are identified as needing a biopsychosocial approach. This means a multidisciplinary treatment approach, including cognitive behavioral therapy. *Comments*: Freely available. Can be used as a screen and an outcome measure. It is meant to be given at the beginning of treatment.
	PHQ **5 minutes**	**Patient Health Questionnaire** http://www.phqscreeners.com/sites/g/files/g10016261/f/201411/English_0.pdf *Measures*: The PHQ is a self-administered version of the PRIME-MD. It screens for somatization and self-evaluation of severity of physical and mood symptoms. There are several versions of the PHQ: PHQ, PHQ-4, PHQ-7, PHQ-9, and PHQ-15. *Validity*: Cross-sectional, Construct, Criterion *Norms and validation:* No norms. Cut-off scores are used. *Comments*: The PHQ is freely available. It is currently in different languages: Czech, Danish, Dutch, English, Finnish, French, German, Hebrew, Hungarian, Italian, Korean, Malay, Mandarin, Norwegian, Polish, Portuguese, Russian, Spanish, Swedish, and Traditional Chinese. Can be used as a screen and outcome measure.
	Neck Disability Index **5 minutes**	**Neck Disability Index (NDI)** http://academic.regis.edu/clinicaleducation/pdf%27s/NDI_with_scoring.pdf *Measures:* Assesses neck functioning. Measures activity limitation, participation restriction, and impairment within ICF classification. Self-administered. It is a validated variation of the Oswestry. It is intended to use with individuals with chronic neck pain, musculoskeletal pain, whiplash injuries, and cervical radiculopathy. *Validity:* Construct

		Norms and validation: Uses cut-off scores. *Comments:* Is useful for predicting progression from acute to chronic neck dysfunction. The NDI may have floor/ceiling effects. The user of the NDI should supplement with another outcome measure. A higher score indicates more reported functional impairment. Can be used as a screen and outcome measure.
	Upper Limb Functional Index **5 minutes**	**Upper Limb Functional Index (ULFI)** https://www.worksafe.vic.gov.au/__data/assets/pdf_file/0003/10956/upper_extremity.pdf *Measures:* Assesses functioning related to upper extremities through 20 items. It is a self-administered screen. Questions are answered on a Likert-scale ranging from extreme difficulty to no difficulty. *Validity:* Construct *Reliability:* High test-retest reliability. Low measurement differences which indicates a high internal consistency. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* The ULFI can be used to assess initial functional, treatment progress and treatment outcome. Can be hand scored. There is an online score calculator found at: https://www.thecalculator.co/health/Upper-Extremity-Functional-Index-(UEFI)-Calculator-955.html
	Lower Extremity Functional Scale **5 minutes**	**Lower Extremity Functional Scale (LEFS)** http://www.mccreadyfoundation.org/documents/LEFS.pdf *Measures*: Self-administered screen comprised of 20 items related to function of the lower limb only. There are no screens for anxiety or depression. It is reported to be used to measure initial function, treatment progress and outcome. *Validity*: Construct and concurrent. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* This item is freely available. The LEFS can be hand scored. An online score calculator is found at: https://www.thecalculator.co/health/Lower-Extremity-Functional-Scale-(LEFS)-Calculator-1020.html Higher scores indicate less functional difficulty. Is validated for patients with TKA, ankle sprains, inpatient and outpatient lower extremity MSK conditions.

	Lower Limb Questionnaire **5 minutes**	**Lower Limb Questionnaire** http://www.aaos.org/research/outcomes/Lower_Limb.pdf Measure: This is a self-administered screen comprised of 7 questions pertaining to lower limb function only. Validity: Content, construct, and concurrent. Comments: Developed by several professional orthopedic organizations. This screen is freely available. It can be used as a screen and outcome measure.
	Foot and Ankle Ability Measure **5 minutes**	**Foot and Ankle Ability Measure (FAAM)** http://www.aptsnc.com/wp-content/uploads/2012/11/Foot-and-Ankle-Ability-Measure.pdf http://www.aaos.org/uploadedFiles/PreProduction/Quality/Measures/Foot%20and%20Ankle%20Ability%20Measure.pdf *Measures:* Self-administered screen pertaining functioning of foot and/or ankle conditions. Has 29 items, with 8 items rated in a sports subscale and 21 items rated in an ADL subscale. Validated for individuals with diabetes and foot and/or ankle conditions. Items are rated on a Likert scale. Sport and ADL subscales are score separately. *Validity:* Content, construct *Norms and validation:* No norms. Uses cut-off scores. *Comments:* The FAAM can be used to assess chronic ankle instability, heel pain/plantar fasciitis, RA and OA of the foot/ankle, sprains, and fractures. Lower scores indicate higher loss of function.
	Patient-Specific Functional Scale **<5 minutes**	**Patient-Specific Functional Scale (PSFS)** *Measures:* Assesses functioning with an orthopedic condition. Has been validated for neck, upper extremity, and knee dysfunction. Measures activity limitation, participation restriction, and impairment within ICF classification. The total score is derived from the sum of activity scores. *Validity:* Construct, concurrent, divergent *Reliability:* High test-retest reliability *Norms and validation*: Concurrent, convergent. *Comments:* The PSFS is free. Floor effect is observed with knee dysfunction. Individuals generally identify activities where substantial impairment exists. There is no space on

		the scale for the individual to note deteriorating functioning. The PSFS has been used with the following conditions: joint replacement, knee dysfunction, low back pain, lower limb amputees, multiple sclerosis, neck dysfunction and whiplash, public symphysis, pain in pregnancy, spinal stenosis, and upper extremity musculoskeletal conditions. Can be used and a screen and outcome measure.
	Orebro Musculoskeletal Pain Questionnaire **5-10 minutes**	**Orebro Musculoskeletal Pain Questionnaire (OMPQ)** *Measures:* Assess the risk than an injured worker will develop a long-term disability or failure to return to work following a musculoskeletal injury. It is comprised of 21 questions. It is identifies psychosocial factors that impact on recovery and return to work. It is completed 4-12 weeks after the injury. *Validity:* Construct, concurrent, convergent, discriminant. *Reliability:* High test-retest, sensitivity, and specificity. *Norms and validation:* *Comments:* Can be used for all body regions, including spine, upper extremities, and lower extremities. Is useful for identifying potential risk factors so that early intervention can take place.

Table A3. Glossary of Psychological Outcome Measures for Assessing Pain, Mood, Sleep Disturbance, and Functioning		
Assessment Task	**Test**	**Description**
PROMIS Measures	***These brief tests are intended for the assessment of pin, mood, sleep disturbance, and functioning, and can be used to track progress in treatment as well as outcome.***	
	PROMIS-29 Profile **5-15 minutes**	**Patient-Reported Outcomes Measurement Information System** http://www.nihpromis.com/?AspxAutoDetectCookieSupport=1#5 *Measures:* Evaluates physical functioning, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity. *Validity measures:* Content, Cross-sectional, & Clinical *Norms and Validation:* Age-based norms, Uses cutoff scores *Comments:* There are PROMIS short forms and Computer Adaptive Test (CAT). Both have been developed by the National Institute of Health and other national organizations. Short forms have 4-10 items. CATs have 3-7. PROMIS short forms and profiles can be administered in a paper and pencil format. In addition, PROMIS measures are available in an iPad app format. There are three main profiles to administer to assess pain, mood, sleep disturbance, and functioning: PROMIS-29, PROMIS- 43, and PROMIS-57. Each of the profiles is administered throughout the treatment process to evaluate treatment progress and outcome. Cutoff scores provide clear-cut data about whether specific issues have resolved. PROMIS measures are available in English and Spanish, with additional language versions currently under development. Users of the PROMIS measures are instructed to not modify any measures since the results from a modified measure will no longer have the same psychometric properties as the original PROMIS measure. Any modifications must be specified in any publications or other public work products. All of the profiles are free. The PROMIS profile-29 are found at: http://www.healthmeasures.net/administrator/components/com_instruments/uploads/PROMIS-29%20Profile%20v2.0%2012-21-2016.pdf The user should check periodically for updated profiles.

	PROMIS-43 **15-25 minutes**	**Patient-Reported Outcomes Measurement Information System** http://www.nihpromis.com/?AspxAutoDetectCookieSupport=1#5 *Measures:* Evaluates physical functioning, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity. *Validity measures:* Content, Cross-sectional, & Clinical *Norms and Validation:* Age-based norms, Uses cutoff scores *Comments:* There are PROMIS short forms and Computer Adaptive Test (CAT). Both have been developed by the National Institute of Health. Short forms have 4-10 items. CATs have 3-7. PROMIS short forms and profiles can be administered in a paper and pencil format. In addition, PROMIS measures are available in an iPad app format. There are three main profiles to administer to assess pain, mood, sleep disturbance, and functioning: PROMIS-29, PROMIS- 43, and PROMIS-57. Each of the profiles is administered throughout the treatment process to evaluate treatment progress and outcome. Cutoff scores provide clear-cut data about whether specific issues have resolved. PROMIS measures are available in English and Spanish, with additional language versions currently under development Users of the PROMIS measures are instructed to not modify any measures since the results from a modified measure will no longer have the same psychometric properties as the original PROMIS measure. Any modifications must be specified in any publications or other public work products. All of the profiles are free. The PROMIS profile-43 is found at: http://www.healthmeasures.net/administrator/components/com_instruments/uploads/PROMIS-43%20Profile%20v2.0%2012-21-2016.pdf The user should check periodically for updated profiles.
	PROMIS-57 **30-40 minutes**	**Patient-Reported Outcomes Measurement Information System** http://www.nihpromis.com/?AspxAutoDetectCookieSupport=1#5 *Measures:* Evaluates physical functioning, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, and pain intensity. *Validity measures:* Content, Cross-sectional, & Clinical *Norms and Validation:* Age-based norms, Uses cutoff scores *Comments:* There are PROMIS short forms and Computer Adaptive Test (CAT). Both have been developed by the National Institute of Health. Short forms have 4-10 items. CATs

		have 3-7. PROMIS short forms and profiles can be administered in a paper and pencil format. In addition, PROMIS measures are available in an iPad app format. There are three main profiles to administer to assess pain, mood, sleep disturbance, and functioning: PROMIS-29, PROMIS- 43, and PROMIS-57. Each of the profiles is administered throughout the treatment process to evaluate treatment progress and outcome. Cutoff scores provide clear-cut data about whether specific issues have resolved. PROMIS measures are available in English and Spanish, with additional language versions currently under development Users of the PROMIS measures are instructed to not modify any measures since the results from a modified measure will no longer have the same psychometric properties as the original PROMIS measure. Any modifications must be specified in any publications or other public work products. All of the profiles are free. The PROMIS profile-57 is found at: http://www.healthmeasures.net/administrator/components/com_instruments/uploads/PROMIS-57%20Profile%20v2.0%2012-21-2016.pdf The user should check periodically for updated profiles.
	NIH Toolbox **1-5 minutes**	**NIH Toolbox Measures** http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox *Measures:* Assesses cognitive, emotional, sensory, and motor functions. However, regarding pain, the NIH Toolbox recommends just two measures which are discussed below. Cook, K.F., Dunn, W., Griffith, J.W., Morrison, M.T., Tanquary, J., Sabata, D., Victorson, D., Carey, L.M., MacDermid, J.C., Dudgeon, B.J. and Gershon, R.C. (2013) 'Pain assessment using the NIH Toolbox', *Neurology*, 80(Issue 11, Supplement 3), pp. S49–S53. doi: 10.1212/wnl.0b013e3182872e80. *Validity measures:* Content, Concurrent, Cross-sectional *Norms and Validation:* No norms, uses cutoff scores *Comments:* The NIH Toolbox uses two measures to assess pain in adults. The first is a single question pertaining to rating pain-intensity on a 0-10 scale. The second is the PROMIS Pain Interference v1.0-Pain Interference 6a. This short-form measure has 6 items. The PROMIS Pain Interference v1.0 6a measure is found at: http://www.healthmeasures.net/administrator/components/com_instruments/u

		ploads/PROMIS%20SF%20v1.0%20-%20Pain%20Interference%206a%206-2-2016.pdf However, PROMIS has four pain interference measures in short form: 4a, 6a, 6b, and 8a. The number is associated with the number of items in each short form. All PROMIS pain short forms are found at: http://www.healthmeasures.net/search-view-measures?task=Search.search PROMIS short forms and profiles can be administered in a paper and pencil format. In addition, PROMIS measures are available in an iPad app format PROMIS measures are available in English and Spanish, with additional language versions currently under development Users of the PROMIS measures are instructed to not modify any measures since the results from a modified measure will no longer have the same psychometric properties as the original PROMIS measure. Any modifications must be specified in any publications or other public work products. All of the profiles are free.
	SF-36 **5-15 minutes**	**36-Item Short-Form Health Survey** http://www.rand.org/health/surveys_tools/mos/36-item-short-form/survey-instrument.html *Measures:* General physical and mental health *Validity measures:* Cross-sectional, Criterion, and Face *Norms and Validation:* SF-36 is the most familiar of a series of related instruments developed through the Medical Outcomes Study initiated by the RAND Corporation. Hypertension and other norms available for original SF-36, which had both acute and standard forms. SF36 v2 has uniform format, and standardized T scores using community norms. RAND 36-Item Health Survey 1.0 includes the same items as those in SF-36, but the recommended scoring algorithm is somewhat different from that of the SF-36. Other forms include the longer HSQ 2.0, and the shorter SF-20, SF-12, SF-12v2, SF-10 and SF-8. *Comments:* Has scoring software. Does not assess depression, anxiety, or somatization. Reading level varies between items, with some items as low as grade 2, and other items as high as grade 12. [1064] *Languages:* English and Spanish, German, French, Chinese, Japanese, and for persons from the following countries: Armenia, Bangladesh, Brazil, Bulgaria, Cambodia, Croatia, Czech Republic, Finland, Greece, Hungary, Iceland, Israel, Korea, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Singapore, Slovak Republic, Tanzania, Turkey, Wales (UK), and Vietnam. Comments: RAND Health developed the SF-36. RAND requires the user to obtain written permission for any changes made to the SF-36. Any publications with changes in the SF-36 and published must clearly note the changes made to the SF-

		36. It must also give written credit to RAND and that the SF-36 was developed as part of the Medical Outcomes Study.
	Quebec Back Pain Disability Questionnaire **5 minutes**	**Dallas Pain Questionnaire** http://scale-library.com/pdf/Dallas_Pain_Questionnaire.pdf *Measures*: Self-questionnaire specific to low back pain. Assess pain and function on daily living. There are four main areas that are assessed: daily activities, professional activities, anxiety/depression, and sociability. This is a self-administered screen. Questions are based on a five-point Likert scale. *Validity*: Face, content, criterion, construct. *Comments*: The scale is available in English and French. The scale is free. Can be used as a screen and outcome measure.
	Dallas Pain Questionnaire **5 minutes**	**Dallas Pain Questionnaire** http://scale-library.com/pdf/Dallas_Pain_Questionnaire.pdf *Measures*: Self-questionnaire specific to low back pain. Assess pain and function on daily living. There are four main areas that are assessed: daily activities, professional activities, anxiety/depression, and sociability. This is a self-administered screen. Questions are based on a five-point Likert scale. *Validity*: Face, content, criterion, construct. *Comments*: The scale is available in English and French. The scale is free.
	Patient-Specific Functional Scale **<5 minutes**	**Patient-Specific Functional Scale (PSFS)** *Measures:* Assesses functioning with an orthopedic condition. Has been validated for neck, upper extremity, and knee dysfunction. Measures activity limitation, participation restriction, and impairment within ICF classification. The total score is derived from the sum of activity scores. *Validity:* Construct, concurrent, divergent *Reliability:* High test-retest reliability *Norms and validation*: Concurrent, convergent. *Comments:* The PSFS is free. Floor effect is observed with knee dysfunction. Individuals generally identify activities where substantial impairment exists. There is no space on the scale for the individual to note deteriorating functioning. The PSFS has been used with the following conditions: joint replacement, knee dysfunction, low back pain, lower limb amputees, multiple sclerosis, neck dysfunction and whiplash, public symphysis, pain in pregnancy, spinal stenosis, and upper extremity musculoskeletal conditions. Can be used and a screen and outcome measure.

	Neck Disability Index **5 minutes**	**Neck Disability Index (NDI)** http://academic.regis.edu/clinicaleducation/pdf%27s/NDI_with_scoring.pdf *Measures:* Assesses neck functioning. Measures activity limitation, participation restriction, and impairment within ICF classification. Self-administered. It is a validated variation of the Oswestry. It is intended to use with individuals with chronic neck pain, musculoskeletal pain, whiplash injuries, and cervical radiculopathy. *Validity:* Construct *Norms and validation:* Uses cut-off scores. *Comments:* Is useful for predicting progression from acute to chronic neck dysfunction. The NDI may have floor/ceiling effects. The user of the NDI should supplement with another outcome measure. A higher score indicates more reported functional impairment. Can be used as a screen and outcome measure.
	Quick DASH **5 minutes**	**QuickDASH (Disabilities of the Arm, Shoulder, and Hand)** http://dash.iwh.on.ca/quickdash *Measures*: Uses 11 items to assess physical function and symptoms in people with musculoskeletal issues in the upper extremity musculoskeletal concerns. It focuses on disability/symptom rating. *Validity: Construct* *Norms and validation:* No norms. Cut-off scores are used. Significant differences in scores with individuals Reporting severe symptoms. *Comments*: Can be hand-scored or scored with an e-tool. The Quick DASH is free provided it is not placed into any product or is sold. Can be used as a screen and outcome measure.
	Simple Shoulder Test **5 minutes**	**Simple Shoulder Test (SST)** http://www.orthop.washington.edu/?q=patient-care/articles/shoulder/simple-shoulder-test.html *Measures*: Utilizes 11 questions to ask about the individual's functioning regarding the shoulder only. This is a self-report tool. *Validation*: Face and cross-sectional *Norms and validation:* No norms. Uses cut-off scores. Comments: It is freely available.

	Upper Limb Functional Index **5 minutes**	**Upper Limb Functional Index (ULFI)** https://www.worksafe.vic.gov.au/__data/assets/pdf_file/0003/10956/upper_extremity.pdf *Measures:* Assesses functioning related to upper extremities through 20 items. It is a self-administered screen. Questions are answered on a Likert-scale ranging from extreme difficulty to no difficulty. *Validity:* Construct *Reliability:* High test-retest reliability. Low measurement differences which indicates a high internal consistency. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* The ULFI can be used to assess initial functional, treatment progress and treatment outcome. Can be hand scored. There is an online score calculator found at: https://www.thecalculator.co/health/Upper-Extremity-Functional-Index-(UEFI)-Calculator-955.html
	Western Ontario Rotator Cuff Index **5 minutes**	**Western Ontario Rotator Cuff Index (WORC)** *Measures:* Assesses rotator cuff function and pain only. It has 21 questions that are visual analog scale items organized into 5 categories: quality of life (Qol), sports/recreation, work, lifestyle, and emotions. Items are rated on a Likert scale. *Validity:* Construct, concurrent, criterion *Reliability:* High test-retest reliability. Low measurement differences which indicates a high internal consistency. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* Has been found empirically to be more response than the SST, QuickDASH, DASH, and SF-36. A higher score is associated with lower level of functioning.
	Patient-Rated Elbow Evaluation **5 minutes**	**Patient-Rated Elbow Evaluation** http://srs-mcmaster.ca/wp-content/uploads/2015/05/English-PREE.pdf Measure: A self-administered questionnaire that asks individuals to rate elbow pain and function. There are no assessment measures of anxiety or depression. Validation: Concurrent, Face, and Content Comments: This screen is freely available.

	Lower Extremity Functional Scale **5 minutes**	**Lower Extremity Functional Scale (LEFS)** http://www.mccreadyfoundation.org/documents/LEFS.pdf *Measures*: Self-administered screen comprised of 20 items related to function of the lower limb only. There are no screens for anxiety or depression. It is reported to be used to measure initial function, treatment progress and outcome. *Validity*: Construct and concurrent. *Norms and validation:* No norms. Uses cut-off scores. *Comments:* This item is freely available. The LEFS can be hand scored. An online score calculator is found at: https://www.thecalculator.co/health/Lower-Extremity-Functional-Scale-(LEFS)-Calculator-1020.html Higher scores indicate less functional difficulty. Is validated for patients with TKA, ankle sprains, inpatient and outpatient lower extremity MSK conditions.
	Lower Limb Questionnaire **5 minutes**	**Lower Limb Questionnaire** http://www.aaos.org/research/outcomes/Lower_Limb.pdf Measure: This is a self-administered screen comprised of 7 questions pertaining to lower limb function only. Validity: Content, construct, and concurrent. Comments: Developed by several professional orthopedic organizations. This screen is freely available. It can be used as a screen and outcome measure.
	Foot and Ankle Outcomes Questionnaire **5-20 minutes**	**Foot and Ankle Outcomes Questionnaire** http://www.aaos.org/research/outcomes/Foot_Ankle.pdf Measures: Pain and functioning related to the foot and ankle only. The questions ask about the individual's pain and functioning in the past week. This screen was developed by the American Academy of Orthopedic Surgeons and other organizations. Although the screen indicates it is related to outcomes, a review of the screen demonstrates that is focused on the individual's current level of pain and functioning. Validation: Convergent and structural Reliability: Internal consistency and test-retest Comments: This questionnaire is freely available in English. It can be given multiple times throughout the treatment process to measure treatment progress and outcomes.

Table A4. Glossary of Psychological Assessment Tests Used for the Biopsychosocial Evaluation of Patients with Chronic Pain	
Test Acronym **Length** **Reading Level**	**Description**
These are brief standardized biopsychosocial tests.	
BBHI 2 **7-12 minutes** **6th grade**	**Brief Battery for Health Improvement 2** http://www.pearsonclinical.com/psychology/products/100000162/brief-battery-for-health-improvement-2-bbhi-2.html *Measures:* Standardized measures of pain, functioning, depression, anxiety, and somatization. Multidimensional pain assessment measures pain intensity, distribution, variability, and tolerability. *Validity measures:* Validity checks for exaggerating, minimizing, and random responding. Items left blank invalidate one scale at a time. *Norms and Validation:* Computerized report references multiple norm groups as indicated, with the primary norms being physical rehabilitation norms (composed of half acute and half chronic pain patients), and community norms. Additional subgroup norms for injury-related pain distribution (head injury, neck injury, upper extremity injury, back injury, lower extremity injury), chronic pain subgroup norms, and subgroup norms for rehabilitation patients recruited to fake good and fake bad. Derived from the BHI 2 test. *Comments:* Has scoring software that plots changes in scores over time with repeat administrations. Uses 17 critical items to screen for concerns such as suicidal ideation, compensation focus, addiction, satisfaction with care, psychosis, home life problems, and sleep disorders. *Languages:* English and Spanish
BSI **10-12 minutes** **6th grade**	**Brief Symptom Inventory** Derogatis, L. R., & Melisaratos, N. (1983). The Brief Symptom Inventory (BSI): An introductory report. Psychological Medicine, 13, 595–605. doi:10.1017/S0033291700048017 *Measures:* Standardized measures of depression, anxiety, hostility, phobic anxiety, obsessive-compulsive, somatization, interpersonal sensitivity, paranoid ideation, psychoticism, and three global measures of distress *Validity measures:* None *Norms and Validation:* Uses community and psychiatric patient norms; derived from SCL-90-R test *Comments:* Has scoring software that plots changes in scores over time with repeat administrations
BSI 18	**Brief Symptom Inventory 18** http://www.pearsonclinical.com/psychology/products/100000638/brief-symptom-inventory-18-bsi-18.html *Measures:* Brief standardized measure of depression, anxiety, and somatization

3-5 minutes **6th grade**	*Validity measures:* None *Norms and Validation:* Uses *oncology* patient norms; derived from SCL-90-R test *Comments:* Norms most appropriate for chronic pain associated *with malignancy*. Unclear how norms apply to injury-related pain. Has scoring software that plots changes in scores over time with repeat administrations.
MPI **or** **WHYMPI** **8-10 minutes** **Reading level unknown**	**Multidimensional Pain Inventory or Westhaven Yale Multidimensional Pain Inventory** https://www.va.gov/PAINMANAGEMENT/docs/WHYMPI.pdf *Measures:* Contains 12 brief standardized measures divided into three groups which assess dimensions of the chronic pain experience, patients' perception of others' response to their pain, and participation in daily activities. Offers separate assessment of limitations in functioning/pain interference. Classifies patients as dysfunctional, interpersonally distressed or adaptive coper. *Validity measures:* None *Norms and Validation:* Developed originally with veterans (majority were male). Current norms based on a broad cross section of patients in the U.S. and Sweden with chronic pain, including back pain, pelvic pain, metastatic disease pain, lupus, and other conditions. *Comments:* Has a substantial research base in chronic pain. Does not assess anxiety or depression. Recent Version 3 of the scale is shorter. Reading level unknown. *Languages:* English, Spanish, French, Dutch, Italian, Japanese, Chinese, Portuguese, Finnish, Icelandic, and Swedish versions
P3 **12-15 minutes** **8th grade**	**Pain Patient Profile** http://www.pearsonclinical.com/psychology/products/100000657/pain-patient-profile-p-3.html *Measures:* Standardized measures of depression, anxiety, and somatization *Validity measures:* Validity measure checks for random or bizarre responding, but does not assess minimizing/exaggerating symptoms *Norms and Validation:* Community and chronic pain norms *Comments:* Has scoring software that plots changes in scores over time with repeat administrations *Languages:* English and Spanish
SF-36 **6-8 minutes** **Variable reading level**	**36-Item Short-Form Health Survey** http://www.rand.org/health/surveys_tools/mos/36-item-short-form/survey-instrument.html *Measures:* General physical and mental health *Validity measures:* None *Norms and Validation:* SF-36 is the most familiar of a series of related instruments developed through the Medical Outcomes Study initiated by the RAND Corporation. Hypertension and other norms available for original SF-36, which had both acute and standard forms. SF36 v2 has uniform format, and standardized T scores using community norms. RAND 36-Item Health Survey 1.0 includes the same items as those in SF-36, but the recommended scoring algorithm is somewhat different from that of the SF-36. Other forms include the longer HSQ 2.0, and the shorter SF-20, SF-12, SF-12v2, SF-10 and SF-8. *Comments:* Has scoring software. Does not assess depression, anxiety, or somatization. Reading level varies between items, with some items as low as grade 2, and other items as high as grade 12. [1064]

	Languages: English and Spanish, German, French, Chinese, Japanese, and for persons from the following countries: Armenia, Bangladesh, Brazil, Bulgaria, Cambodia, Croatia, Czech Republic, Finland, Greece, Hungary, Iceland, Israel, Korea, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Singapore, Slovak Republic, Tanzania, Turkey, Wales (UK), and Vietnam.
SCL-90-R **12-15 minutes** **6th grade**	**Symptom Checklist 90 – Revised** http://www.pearsonclinical.com/psychology/products/100000645/symptom-checklist-90-revised-scl-90-r.html Measures: Standardized measures of depression, anxiety, hostility, phobic anxiety, obsessive-compulsive, somatization, interpersonal sensitivity, paranoid ideation, psychoticism, and three global measures of distress Validity measures: None Norms and Validation: Four norm groups available: adult psychiatric outpatients, adult psychiatric inpatients, adult non-patient, and adolescent non-patient; derived from SCL-90-R test Comments: Has scoring software that plots changes in scores over time with repeat administrations

Table A5. Glossary of Standardized Psychological Tests Used for the Psychopathology Evaluation of Patients with Chronic Pain		
Description		
These are standardized psychological tests for the assessment of patients with psychopathology and who make threats		
Psychological Assessment of Psychopathology	***These are comprehensive measures for assessing patients with psychopathology and who make threats***	
	BHI 2	**See Table A6**
	Hare Psychopathy Checklist – Revised	**Hare Psychopathy Checklist – Revised** http://www.hare.org/scales/pclr.html Can be used to help assess the degree to which an individual exhibits severe antisocial traits in the form of a prototypical violent psychopath. May be useful if assessing patients who are making threats. Takes up to 3 hours of professional time.
	MMPI-2	**See Table A6**
	MMPI-2-RF	**See Table A6**

Table A6. Glossary of Psychological Assessment Tests Used for the Biopsychosocial Evaluation of Patients with Chronic Pain		
Description		
These are standardized biopsychosocial psychological tests.		
Comprehensive Chronic Pain Psychological Assessment	***These are comprehensive measures for assessing patients with chronic pain***	
	BHI 2 **25-35 minutes** **6th grade**	**Battery for Health Improvement 2** http://www.pearsonclinical.com/psychology/products/100000095/battery-for-health-improvement-2-bhi-2.html *Measures:* Standardized measures include 16 major scales and 40 minor scales. Multidimensional pain assessment assesses extreme risk factors (dangerousness to self and others, psychosis, etc.), assesses psychosocial risk believed to be associated with a poor outcome following rehabilitation or surgical interventions, substance abuse, and opioid vulnerabilities, and also assesses both catastrophizing and kinesiophobia. Additionally, assesses 21 pain-related variables including pain intensity, variability, distribution, and tolerability. Assesses depression, anxiety, hostility, somatization, functioning, substance abuse, victimization, job dissatisfaction, anger at physicians, borderline, dependent coping, compensation focus, perseverance, and other variables. *Validity measures:* Two measures assess exaggerating, two assess minimizing, and one assesses random/bizarre responding. Items left blank invalidate one scale at a time rather than the whole test. *Norms and Validation:* Computerized report references multiple norm groups as indicated, with the primary norms being physical rehabilitation norms (composed of half acute and half chronic pain patients), and community norms. Additional subgroup norms for injury-related pain distribution (head injury, neck injury, upper extremity injury, back injury, lower extremity injury), chronic pain subgroup norms, and subgroup norms for rehabilitation patients recruited to fake good and fake bad. *Comments:* The development of this test was based on the "Vortex Paradigm" biopsychosocial theory. It has scoring software that plots changes in scores over time with repeat administrations *Languages:* English and Spanish
	MBMD	**Millon Behavioral Medicine Diagnostic** http://www.millon.net/instruments/MBMD.htm *Measures:* Total of 35 standardized scales include 5 psychiatric indications scales (anxiety, depression, cognitive dysfunction, emotional lability and

	20-30 minutes **6th grade**	guardedness), 11 coping scales, 6 negative health habits scales, 6 stress moderators scales, 5 prognostic scales, and 2 management scales. Scales intended to identify psychiatric and problematic behavioral comorbidities that may affect health management and compliance. *Validity measures:* One scale measures exaggerating, one minimizing; one bidirectional scale measures both exaggerating and minimizing, and one assesses random responding. *Norms and Validation:* Three patient norm groups, chronic illness (primarily heart disease, diabetes, HIV, neurological, 9% with chronic pain, but no identified physical rehabilitation patients), bariatric patient, and pain patient norms. *Comments:* Base rate scoring attempts to adjust test findings to approximate the actual base rates of psychological disorders observed in medical patients. Although the MBMD has pain norms, the general medical norms are used to score the test's pain prognosis algorithms, not the pain norms. Computer scored. *Languages:* English and Spanish.
	MCMI I-V **25-30 minutes** **8th grade**	**Millon Clinical Multiaxial Inventory IV** http://www.millonpersonality.com/inventories/MCMI-IV/ *Measures:* 24 standardized scales keyed to the DSM-5 diagnoses, including affective disorders, psychosis, and substance use, with separate scales for each type of personality disorder. *Validity measures:* One scale measures exaggerating, one minimizing; one bidirectional scale measures both exaggerating and minimizing, and one assesses random responding. *Norms and Validation:* Inpatient and outpatient psychiatric patients. *Comments:* Base rate scoring attempts to adjust test findings to approximate the actual base rates of psychological disorders in the psychiatric population. Computer scored. *Languages:* English and Spanish.
	MMPI 2 **70-90 minutes** **6th grade**	**Minnesota Multiphasic Personality Inventory 2** https://www.upress.umn.edu/test-division/minnesotareport/minnesota-reports-overview *Measures:* Complex test with 126 official standardized scales, measuring a wide range of psychopathology. In addition to the 10 original MMPI clinical scales, scales were generated by a variety of methods (e.g., content analysis, factor analysis and others) and for a variety of purposes (assessing addictive tendencies and health concerns). Assesses depression, anxiety, somatization, addictive tendencies, psychosis, characterological tendencies, social support, and numerous other psychiatric conditions. *Validity measures:* Multiple validity measures assess patient responding. Three scales measure exaggerated, bizarre, or random responding; three

		measure minimizing; two measure contradictory responses. Also assessed is the number of items left blank on test, and percent left blank on each scale. *Norms and Validation:* Community norms. *Comments:* Computer scored. Several scales include physical symptoms that could be attributable to injury, illness, or medication side effects. [1065, 1066] This increases the risk of false positive psychological scores when medical patients report their symptoms. A long test, but despite its length does not measure several variables important for chronic pain assessment, including pain, functioning, and job dissatisfaction, so often needs to be paired with other tests. The most researched psychological test, a major revision (MMPI RF) is scheduled for release in 2008, and is substantially different from MMPI 2. [1067-1071] *Languages:* English, Spanish, Hmong, and French versions.
	MMPI 2 RF **40-50 minutes** **6th grade**	**Minnesota Multiphasic Personality Inventory 2 Revised Form** http://www.pearsonclinical.com/psychology/products/100000631/minnesota-multiphasic-personality-inventory-2-rf-mmpi-2-rf.html *Measures:* Revised version of the MMPI-2 with 51 standardized scales, measuring a wide range of psychopathology. Assesses somatic/cognitive dysfunction, emotional dysfunction, thought dysfunction, behavioral dysfunction, interpersonal functioning, and interests. *Validity measures:* Nine validity measures assess patient responding. Five scales measure exaggerated responding; two measure minimizing; two measure contradictory responses, and one assesses non-responsiveness. Also assessed is the percent left blank on each scale. *Norms and Validation:* Norms on 20 groups are available, including chronic pain and spine surgery candidates. *Comments:* Computer scored. Substantially shorter than the MMPI-2, but still longer than all other tests reviewed here. While it has many psychometric improvements over the MMPI-2 [1111], the MMPI 2 RF has been critiqued as having more of a psychiatric focus than the MMPI 2, and thus less capable of assessing medical patients [1112] *Languages:* English, Spanish and French versions.
	PAI **50-60 minutes** **4th grade**	**Personality Assessment Inventory** http://www.wpspublish.com/store/p/2893/personality-assessment-inventory-pai *Measures:* Standardized assessment of a broad cross-section of affective, characterological and psychotic conditions with 18 major scales and 31 subscales. *Validity measures:* One scale measures exaggerating, one minimizing, one random responding, and one assesses contradictory responses. *Norms and Validation:* Community and psychiatric norms.

		Comments: A comprehensive personality test that is significantly shorter than MMPI 2. Some scales, and in particular the somatization scale, include physical symptoms that could be attributable to injury or medication side effects. This increases the risk of false positive psychological scores when medical patients report their symptoms.
	Hare Psychopathy Checklist – Revised	**Hare Psychopathy Checklist – Revised** http://www.hare.org/scales/pclr.html Can be used to help assess the degree to which an individual exhibits severe antisocial traits in the form of a prototypical violent psychopath. May be useful if assessing patients who are making threats. Takes up to 3 hours of professional time.

Table A7. Glossary of Neuropsychological Psychological Measures for Assessing Pain and Cognitive Functioning		
Assessment Task	**Test**	**Description**
Cognitive Functioning Assessment	***These tests are intended for cognitive assessment.*** Note: *Some chronic pain patients report being unable to perform cognitive workplace functions secondary to medication side effects, lack of sleep, pain severity, or emotional distress. Cognitive tests generally do not include validity measures. They are almost impossible to fake good, but easy to fake bad. Thus, the test administrator will often need to administer 1 to2 psychological tests that evaluate sincerity of test effort and to rule out the potential for symptom exaggeration.*	
	GAMA **25 minute timed test**	**General Ability Measure for Adults** http://www.pearsonclinical.com/psychology/products/100000200/general-ability-measure-for-adults-gama.html *Measures:* Provides a culture-free estimate of general ability based on the scores on 4 subtest scales: matching, analogies, sequences, and construction.
	RBANS-Update **20- 30 minutes**	**Repeatable Battery for the Assessment of Neuropsychological Status-Update** http://www.pearsonclinical.com/psychology/products/100000726/repeatable-battery-for-the-assessment-of-neuropsychological-status-update-rbans-update.html?origsearchtext=RBANS Randolph, C., Tierney, M. C., Mohr, E., & Chase, T. N. (1998). The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary clinical validity. *The Journal of Clinical and Experimental Neuropsychology* 20, 310–319. *Measures:* Cognitive decline in individuals who have experienced stroke, head injury, dementia, or neurological injury or disease. Measures neuropsychological status in format and content similar to Wechsler tests. It measures attention, language, memory, and visuospatial/constructional abilities. *Validity:* Concurrent, criterion, construct *Norms and Validation:* Age, genders norms, uses *Comments:* The RBANS is a standardized test which assesses a variety of types of cognitive functioning. It has two forms of the test: A and B. The RBANS-Update can provide a measure of daily functioning.

		These standardized neuropsychological tests are intended to evaluate multiple types of cognitive of functioning.
Tests of Cognitive Ability	**WASI-II** **15-30 minutes**	**Wechsler Abbreviated Scale of Intelligence-II** http://wechslertest.com/ *Measures:* Provides an abbreviated measurement of adult intelligence. These abbreviated scores are estimates of functioning since only the full administration of the WAIS-IV can provide full functioning scores. *Validity: Concurrent, criterion, construct* *Comments*: Can select either two-subtests or four-subtests to administer. Test administration time approximately 15 minutes for 2 subtests; 30 minutes for 4 subtests.
	WAIS-IV **60-90 minutes**	**Wechsler Adult Intelligence Scale IV** http://wechslertest.com/ *Measures:* Adult intellectual ability and cognitive strengths and weaknesses. WAIS-IV and WMS-IV are the only co-normed ability-memory instruments. *Validity:* Criterion, construct, concurrent, predictive, convergent, and divergent. *Norms and Validation measures:* Co-normed with the WMS-IV. Age norms *Comments:* The WAIS-IV is a standardized test that evaluates cognitive and performance functioning. It has high internal consistency and re-test reliability. It can provide an estimate of premorbid intellectual functioning.
	WMS-IV **45-60 minutes**	**Wechsler Memory Scale IV** https://www.pearsonclinical.ca/en/products/product-master/item-110.html *Measures:* Assessment of learning and memory functioning of older adolescents and adults. Measures visual and auditory memory, immediate vs. delayed memory, and free recall vs. cued recall as well as recognition. *Validity:* Criterion, construct, concurrent, predictive, convergent, and divergent. *Norms and Validation:* Co-normed with the WAIS-IV. Age norms. *Comments:* The WMS-IV is a standardized test that evaluates cognitive and performance functioning. It has excellent internal consistency and re-test reliability. It can provide an estimate of premorbid intellectual functioning.

	WRAT-4 **35-45 minutes**	**Wide Range Achievement Test 4** http://www.pearsonclinical.com/education/products/100001722/wide-range-achievement-test-4--wrat4.html *Measures:* Basic academic skills of reading, spelling, and math computation. This edition has a new measurement of reading achievement. Age-based norms have been extended into age 94. Has excellent internal consistency and reliability. Has been validated against multiple other cognitive psychological tests.

Table A8. Glossary of Psychological Assessment Tests Used for the Symptom Exaggeration and Malingering of Patients with Chronic Pain		
Description		
These are standardized multidimensional psychological tests.		
Standardized Psychological Assessment for Symptom Exaggeration and Malingering	***These are comprehensive measures for assessing symptom exaggeration in patients with chronic pain. A minimum of two effort tests must be used to better assess for suboptimal effort or malingering.***	
	MPS **20 minutes**	**Malingering Probability Scale** http://www.wpspublish.com/store/p/2869/malingering-probability-scale-mps *Measures*: Assessment of symptom exaggeration or malingering of psychological conditions of depression, anxiety, PTSD, schizophrenia *Norms*: Gender, age, educational level and region. Validation: Specifically validated with workers' compensation claimants.
	SIMS **15 minutes**	**Structured Inventory of Malingered Symptomology** http://www4.parinc.com/Products/Product.aspx?ProductID=SIMS *Measures*: Assesses for malingered psychopathology and cognitive concerns. 75 true/false items. It evaluates malingered psychosis, low intelligence, neurologic impairment, affective disorders, and amnestic disorders. An overall score for probable malingering is obtained. Is used to evaluate disability and workers' compensation issues. *Validity*: Cross-validation, concurrent, criterion, discriminant. *Reliability:* Excellent, test-retest. *Norms and validation:* Norms for cognitively intact individuals as well as specific clinical groups with cognitive impairment, aphasia, traumatic brain injury, and dementia.

		Comments: Cut-off scores for three groups: malingerers, psychiatric, and non-clinical. The SIMS can be hand or computer scored.
	TOMM **15-20 minutes**	**Test of Memory Malingering** http://www.mhs.com/product.aspx?gr=cli&id=overview&prod=tomm *Measures*: Used to assess whether an individual is falsifying symptoms of memory impairment. Assesses faking of memory complaints. Does not assess malingering of pain or musculoskeletal disability symptoms. Hand or computer scored. *Validity:* Construct, concurrent, convergent, divergent. *Norms and validation:* Norms for cognitively intact, cognitively impaired, and malingering individuals. *Comments:* Cutoff scores are used to evaluate for feigned cognitive impairment. Excellent specificity for individuals with chronic pain. Sensitivity is increased with usage of the Albany Consistency Index (ACI).

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Malingering

Aronoff, G. M., et al. (2007). "Evaluating malingering in contested injury or illness." Pain Pract **7**(2): 178-204.

> An interdisciplinary task force of physicians and neuropsychologists with advanced training in impairment and disability assessment provided a review of the literature on malingering in chronic pain, medical disorders, and mental/cognitive disorders. Our review suggests that treating health care providers often do not consider malingering, even in cases of delayed recovery involving work injuries or other personal injuries, where there may be a significant incentive to feign or embellish symptoms or delay recovery. This report discusses the implications of this issue and offers recommendations to evaluating physicians and other health care professionals.

Buddin, W. H., Jr., et al. (2014). "An examination of the frequency of invalid forgetting on the Test of Memory Malingering." Clin Neuropsychol **28**(3): 525-542.

> The Test of Memory Malingering (TOMM) is the most used performance validity test in neuropsychology, but does not measure response consistency, which is central in the measurement of credible presentation. Gunner, Miele, Lynch, and McCaffrey (2012) developed the Albany Consistency Index (ACI) to address this need. The ACI consistency measurement, however, may penalize examinees, resulting in suboptimal accuracy. The Invalid Forgetting Frequency Index (IFFI), created for the present study, utilizes an algorithm to identify and differentiate learning and inconsistent response patterns across TOMM trials. The purpose of this study was to assess the diagnostic accuracy of the ACI and IFFI against a reference test (Malingered Neurocognitive Dysfunction criteria), and to compare both to the standard TOMM indexes. This retrospective case-control study used 59 forensic cases from an outpatient clinic in Southern Kansas. Results indicated that sensitivity, negative predictive value, and overall accuracy of the IFFI were superior to both the TOMM indexes and ACI. Logistic regression odds ratios were similar for TOMM Trial 2, Retention, and IFFI (1.25, 1.24, 1.25, respectively), with the ACI somewhat lower (1.18). The IFFI had the highest rate of group membership predictions (79.7%). Implications and limitations of the present study are discussed.

Chafetz, M. (2011). "Reducing the probability of false positives in malingering detection of Social Security disability claimants." Clin Neuropsychol **25**(7): 1239-1252.

> The Symptom Validity Scale (SVS) for low-functioning individuals (Chafetz, Abrahams, & Kohlmaier, 2007) employs embedded indicators within the Social Security Psychological Consultative Examination (PCE) to derive a score validated for malingering against two criterion tests: Test of Memory Malingering (TOMM) and Medical Symptom Validity Test (MSVT). When any symptom validity test is used with Social Security claimants there is a known rate of mislabeling (1-specificity), essentially calling a performance biased (invalid) when it is not, also known as a false-positive error. The great costs of mislabeling an honest claimant necessitated the present study, designed to show how multiple positive findings reduce the potential for mislabeling. This study utilized a known-groups design to address the impact of using multiple embedded indicators within the SVS on the diagnostic probability of malingering. Using four SVS components, Sequence, Ganser, and Coding errors, along with Reliable Digit Span (RDS), the positive predictive power was computed directly or by the chaining of likelihood ratios. The posterior probability of malingering increased from one to two to three failed indicators. With three failed indicators, there were

essentially no false positive errors, and the total SVS score was in the range consistent with Definite Malingering, as shown in Chafetz et al. (2007). Thus, in a typical PCE when an examiner might have only a few embedded indicators, more confidence in a diagnosis of malingering might be obtained with a finding of multiple failures.

Denning, J. H. (2014). "Combining the test of memory malingering trial 1 with behavioral responses improves the detection of effort test failure." Appl Neuropsychol Adult **21**(4): 269-277.

Validity measures derived from the Test of Memory Malingering Trial 1 (TOMM1) and errors across the first 10 items of TOMM1 (TOMMe10) may be further enhanced by combining these scores with "embedded" behavioral responses while patients complete these measures. In a sample of nondemented veterans (n = 151), five possible behavioral responses observed during completion of the first 10 items of the TOMM were combined with TOMM1 and TOMMe10 to assess any increased sensitivity in predicting Medical Symptom Validity Test (MSVT) performance. Both TOMM1 and TOMMe10 alone were highly accurate overall in predicting MSVT performance (TOMM1 [area under the curve (AUC)] = .95, TOMMe10 [AUC] = .92). The combination of TOMM measures and behavioral responses did not increase overall accuracy rates; however, when specificity was held at approximately 90%, there was a slight increase in sensitivity (+7%) for both TOMM measures when combined with the number of "point and name" responses. Examples are provided demonstrating that at a given TOMM score (TOMM1 or TOMMe10), with an increase in "point and name" responses, there is an incremental increase in the probability of failing the MSVT. Exploring the utility of combining freestanding or embedded validity measures with behavioral features during test administration should be encouraged.

Easton, S. and L. Akehurst (2011). "Tools for the detection of lying and malingering in the medico-legal interview setting." Med Leg J **79**(Pt 3): 103-108.

Egeland, J., et al. (2015). "Types or modes of malingering? A confirmatory factor analysis of performance and symptom validity tests." Appl Neuropsychol Adult **22**(3): 215-226.

Recently, the dichotomy between performance validity tests (PVT) and symptom validity tests (SVT) has been suggested to differentiate between invalid performance and invalid self-report, respectively. PVTs are typically used to identify malingered cognitive impairment, while SVTs identify malingered psychological or somatic symptoms. It is assumed that people can malinger different types of problems, but the impact of modes of reporting invalidly has been largely unexplored. A mixed neurological sample (n = 130) was tested with the Test of Memory Malingering, the Forced Recognition part of the California Verbal Learning Test, and the self-report Structured Inventory of Malingered Symptoms (SIMS). Confirmatory factor analyses testing both method- and content-based factor models found best fit for the method-based division. Regression analyses of other self-rating and performance-based tests provided further support for the importance of type of methods used to collect information. While acknowledging the types of symptoms malingered, the clinician is advised also to consider how information is gathered by using both PVTs and SVTs. SIMS is a good candidate for a stand-alone SVT, although the utility of the Low Intelligence subscale is questionable as a validity measure.

Green, P. (2011). "Comparison between the Test of Memory Malingering (TOMM) and the Nonverbal Medical Symptom Validity Test (NV-MSVT) in adults with disability claims." Appl Neuropsychol **18**(1): 18-26.

In this study, the Nonverbal Medical Symptom Validity Test (NV-MSVT; Green, 2008) and the Test of Memory Malingering (TOMM; Tombaugh, 1996) were given to a consecutive series of outpatients undergoing disability assessment. No cases of moderate to severe traumatic brain injury (TBI) failed the easy NV-MSVT subtests or the TOMM. However, 26% of the mild TBI group failed the NV-MSVT and 10% failed the TOMM. More than 10% of the whole sample passed the TOMM but failed the NV-MSVT. Using profile analysis, the NV-MSVT has been shown to have a zero false-positive rate in three independent groups of patients with severe cognitive impairment arising from dementia. The more severe the actual

cognitive impairment, the more likely it is that false positives for poor effort will occur. Therefore, using the same criteria, we would also expect zero false positives in people with much less severe impairment, such as mild TBI. Those in the current study who passed the TOMM and failed the NV-MSVT had profiles that were not characteristic of people with actual severe impairment. Instead, they were of the paradoxical type seen in simulators. The results suggest that the NV-MSVT is considerably more sensitive to poor effort than the TOMM, if the conventional cutoff is used to define TOMM failure.

Greve, K. W., et al. (2006). "Classification accuracy of the Test of Memory Malingering in persons reporting exposure to environmental and industrial toxins: Results of a known-groups analysis." Arch Clin Neuropsychol **21**(5): 439-448.

This study used a known-groups design to examine the classification accuracy of the Test of Memory Malingering in detecting cognitive malingering in patients claiming cognitive deficits due to exposure to environmental and industrial toxins. Thirty-three patients who met Slick et al. criteria for Malingered Neurocognitive Dysfunction were compared to 17 toxic exposure patients negative for evidence of malingering, 14 TBI patients and 22 memory disorder patients, both groups without incentive. The original cutoffs (<45) for Trial 2 and Retention demonstrated perfect specificity (0% false positive error rate) and impressive sensitivity (>50%). These findings indicate the TOMM can be used with confidence as an indicator of negative response bias in cases of cognitive deficits attributed to exposure to alleged neurotoxic substances.

Greve, K. W., et al. (2006). "Classification accuracy of the test of memory malingering in traumatic brain injury: results of a known-groups analysis." J Clin Exp Neuropsychol **28**(7): 1176-1190.

This study used a known-groups design to determine the classification accuracy of the Test of Memory Malingering (Tombaugh, 1996, 1997) in detecting cognitive malingering in traumatic brain injury (TBI). Forty-one of 161 TBI patients met Slick, Sherman, and Iverson (1999) criteria for Malingered Neurocognitive Dysfunction. Twenty-two no-incentive memory disorder patients were also included. The original cutoffs (<45) for Trial 2 and Retention demonstrated excellent specificity (less than a 5% false positive error rate) and impressive sensitivity (greater than 45%). However, these cutoffs are actually conservative in the context of mild TBI. Over 90% of the non-MND mild TBI sample scored 48 or higher on the Retention Trial and none scored less than 46 while 60% of the MND patients claiming mild TBI were detected at those levels. Trial 1 also demonstrated excellent classification accuracy. Application of these data to clinical practice is discussed.

Greve, K. W., et al. (2009). "Prevalence of malingering in patients with chronic pain referred for psychologic evaluation in a medico-legal context." Arch Phys Med Rehabil **90**(7): 1117-1126.

OBJECTIVE: To provide an empirical estimate of the prevalence of malingered disability in patients with chronic pain who have financial incentive to appear disabled. DESIGN: Retrospective review of cases. SETTING: A private neuropsychologic clinic in a southeastern metropolitan area. PARTICIPANTS: Consecutive patients (N=508) referred for psychologic evaluation related to chronic pain over a 10-year period (1995-2005). INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Prevalence of malingering was examined using 2 published clinical diagnostic systems (Malingered Pain-Related Disability and Malingered Neurocognitive Dysfunction) as well as statistical estimates based on well validated indicators of malingering. RESULTS: The prevalence of malingering in patients with chronic pain with financial incentive is between 20% and 50% depending on the diagnostic system used and the statistical model's underlying assumptions. Some factors associated with the medico-legal context such as the jurisdiction of a workers' compensation claim or attorney representation were associated with slightly higher malingering rates. CONCLUSIONS: Malingering is present in a sizable minority of patients with pain seen for potentially compensable injuries. However, not all excess pain-related disability is a result of malingering. It is important not to diagnose malingering reflexively on the basis of limited or unreliable findings. A diagnosis of malingering should be explicitly based on a formal diagnostic system.

Greve, K. W., et al. (2009). "Prevalence of malingering in patients with chronic pain referred for psychologic evaluation in a medico-legal context." Arch Phys Med Rehabil **90**(7): 1117-1126.

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Gunner, J. H., et al. (2012). "The Albany Consistency Index for the Test of Memory Malingering." Arch Clin Neuropsychol **27**(1): 1-9.

> The determination of examinee effort is an important component of a neuropsychological evaluation and relies heavily on the use of symptom validity tests (SVTs) such as the Test of Memory Malingering (TOMM) and the Word Memory Test (WMT). Diagnostic utility of SVTs varies. The sensitivity of traditional TOMM criteria to suboptimal effort is low. An index of response consistency across three trials of the TOMM was developed, denoted the Albany Consistency Index (ACI). This index identified a large proportion of examinees classified as optimal effort using traditional TOMM interpretive guidelines but suboptimal effort using the WMT profile analysis. In addition, previous research was extended, demonstrating a relationship between examinee performance on SVTs and neuropsychological tests. Effort classification using the ACI predicted the performance on the Global Memory Index from the Memory Assessment Scales. In conclusion, the ACI was a more sensitive indicator of suboptimal effort than traditional TOMM interpretive guidelines.

Henry, G. K., et al. (2006). "The Henry-Heilbronner Index: a 15-item empirically derived MMPI-2 subscale for identifying probable malingering in personal injury litigants and disability claimants." Clin Neuropsychol **20**(4): 786-797.

> A new 15-item MMPI-2 subscale, the Henry-Heilbronner Index (HHI), representing a "pseudosomatic factor," was empirically derived from both the 43-item Lees-Haley Fake Bad Scale (FBS) and the 17-item Shaw and Matthews' Pseudoneurologic Scale (PNS). The HHI was superior to both the FBS and PNS in identification of symptom exaggeration in personal injury litigants and disability claimants compared to non-litigating head-injured controls. Logistic regression analyses revealed that a cutscore of > or = 8 on the HHI was associated with good specificity (89%) and sensitivity (80%). These results suggest that the HHI may be useful in identifying personal injury litigants and disability claimants who exaggerate, overreport, or malinger physical symptoms on the MMPI-2 related to their current health and/or litigation status.

Hilsabeck, R. C., et al. (2011). "Use of Trial 1 of the Test of Memory Malingering (TOMM) as a screening measure of effort: suggested discontinuation rules." Clin Neuropsychol **25**(7): 1228-1238.

> Trial 1 of the Test of Memory Malingering (TOMM) has been suggested as a screening tool, with several possible cut-off scores proposed. The purpose of the present study was to replicate the utility of previously suggested cut-off scores and to characterize neuropsychological profiles of persons who "pass" the TOMM

but obtain Trial 1 scores < 45 and of persons with cognitive disorders. A total of 229 veterans were administered the TOMM as part of a neuropsychological evaluation. Trial 1 scores >/= 41 and </= 25 showed good utility as discontinuation scores for adequate and poor effort, respectively, beyond which administration of additional trials were unnecessary. Findings suggest better Trial 1 performance is significantly related to better speeded mental flexibility and memory.

Iverson, G. L. (2006). "Ethical issues associated with the assessment of exaggeration, poor effort, and malingering." Appl Neuropsychol **13**(2): 77-90.

The use of effort tests is standard practice in forensic neuropsychology. There is a tremendous amount of good information available in test manuals and the research literature regarding the proper and responsible use of these tests. However, it is clear that there are numerous ethical issues and considerations associated with the assessment of exaggeration, poor effort, and malingering. Many of these issues are discussed, and recommendations are provided.

Iverson, G. L. (2007). "Identifying exaggeration and malingering." Pain Pract **7**(2): 94-102.

Iverson, G. L., et al. (2007). "Test of Memory Malingering (TOMM) scores are not affected by chronic pain or depression in patients with fibromyalgia." Clin Neuropsychol **21**(3): 532-546.

Neuropsychologists routinely give effort tests, such as the Test of Memory Malingering (TOMM). When a person fails one of these tests, the clinician must try to determine whether the poor performance was due to suboptimal effort or to chronic pain, depression, or other problems. Participants were 54 community-dwelling patients who met American College of Rheumatology criteria for fibromyalgia (FM). In addition to the TOMM, they completed the Beck Depression Inventory-Second Edition, Multidimensional Pain Inventory-Version 1, Oswestry Disability Index-2.0, British Columbia Cognitive Complaints Inventory, and the Fibromyalgia Impact Questionnaire. The majority endorsed at least mild levels of depressive symptoms (72%), and 22% endorsed "severe" levels of depression. The average scores on the TOMM were 48.8 (SD = 1.9, range = 40-50) for Trial 1, 49.8 (SD = 0.5, range = 48-50) for Trial 2, and 49.6 (SD = 0.9, range = 45-50) for Retention. Despite relatively high levels of self-reported depression, chronic pain, and disability, not a single patient failed the TOMM. In this study, the TOMM was not affected by chronic pain, depression, or both.

Jelicic, M., et al. (2011). "Detecting coached feigning using the Test of Memory Malingering (TOMM) and the Structured Inventory of Malingered Symptomatology (SIMS)." J Clin Psychol **67**(9): 850-855.

Undergraduate students were administered the Test of Memory Malingering (TOMM) and the Structured Inventory of the Malingered Symptomatology (SIMS) and asked to respond honestly, or instructed to feign cognitive dysfunction due to head injury. Before both instruments were administered, symptom-coached feigners were provided with some information about brain injury, while feigners who received a mix of symptom-coaching and test-coaching were given the same information plus advice on how to defeat symptom validity tests. Results show that, although the accuracy of both instruments appears to be somewhat reduced by a mix of symptom coaching and test coaching, the TOMM and SIMS are relatively resistant to different kinds of coaching.

Lange, R. T., et al. (2010). "Influence of poor effort on self-reported symptoms and neurocognitive test performance following mild traumatic brain injury." J Clin Exp Neuropsychol **32**(9): 961-972.

When considering a diagnosis of postconcussion syndrome, clinicians must systematically evaluate and eliminate the possible contribution of many differential diagnoses, comorbidities, and factors that may cause or maintain self-reported symptoms long after mild traumatic brain injury (MTBI). One potentially significant contributing factor is symptom exaggeration. The purpose of the study is to examine the influence of poor effort on self-reported symptoms (postconcussion symptoms and cognitive complaints)

and neurocognitive test performance following MTBI. The MTBI sample consisted of 63 referrals to a concussion clinic, evaluated within 5 months post injury (M = 2.0, SD = 1.0, range = 0.6-4.6), who were receiving financial compensation from the Workers' Compensation Board. Participants completed the Post-Concussion Scale (PCS), British Columbia Cognitive Complaints Inventory (BC-CCI), selected tests from the Neuropsychological Assessment Battery Screening Module (S-NAB), and the Test of Memory Malingering (TOMM). Participants were divided into two groups based on TOMM performance (15 fail, 48 pass). There were significant main effects and large effect sizes for the PCS (p = .002, d = 0.79) and BC-CCI (p = .011, d = 0.98) total scores. Patients in the TOMM fail group scored higher than those in the TOMM pass group on both measures. Similarly, there were significant main effects and/or large effect sizes on the S-NAB. Patients in the TOMM fail group performed more poorly on the Attention (p = .004, d = 1.26), Memory (p = .006, d = 1.16), and Executive Functioning (p > .05, d = 0.70) indexes. These results highlight the importance of considering the influence of poor effort, in conjunction with a growing list of factors that can influence, maintain, and/or mimic the persistent postconcussion syndrome.

Lange, R. T., et al. (2012). "Influence of poor effort on neuropsychological test performance in U.S. military personnel following mild traumatic brain injury." J Clin Exp Neuropsychol **34**(5): 453-466.

The purpose of this study was to examine the influence of poor effort on neuropsychological test performance in military personnel following mild traumatic brain injury (MTBI). Participants were 143 U.S. service members who sustained a TBI, divided into three groups based on injury severity and performance on the Word Memory Test and four embedded markers of poor effort: MTBI-pass (n = 87), MTBI-fail (n = 21), and STBI-pass (n = 35; where STBI denotes severe TBI). Patients were evaluated at the Walter Reed Army Medical Center on average 3.9 months (SD = 3.4) post injury. The majority of the sample was Caucasian (84.6%), was male (93.0%), and had 12+ years of education (96.5%). Measures included the Personality Assessment Inventory (PAI) and 13 common neurocognitive measures. Patients in the MTBI-fail group performed worse on the majority of neurocognitive measures, followed by the Severe TBI-Pass group and the MTBI-pass group. Using a criterion of three or more low scores <10th percentile, the MTBI-fail group had the greatest rate of impairment (76.2%), followed by the Severe TBI-Pass group (34.3%) and MTBI-pass group (16.1%). On the PAI, the MTBI-fail group had higher scores on the majority of clinical scales (p < .05). There were a greater number of elevated scales (e.g., 5 or more elevated mild or higher) in the MTBI-fail group (71.4%) than in the MTBI-pass group (32.2%) and Severe TBI-Pass group (17.1%). Effort testing is an important component of postacute neuropsychological evaluations following combat-related MTBI. Those who fail effort testing are likely to be misdiagnosed as having severe cognitive impairment, and their symptom reporting is likely to be inaccurate.

Lynch, W. J. (2004). "Determination of effort level, exaggeration, and malingering in neurocognitive assessment." J Head Trauma Rehabil **19**(3): 277-283.

OBJECTIVES: This article presents a review of the field of effort level determination in TBI assessment as well as how to determine which effort level measure is most appropriate for common assessment situations. The importance of effort level assessment in forensic settings, and also in assessments conducted in both diagnostic and rehabilitation programs, which rely on test performances to develop treatment plans or to measure progress and outcome, is discussed. METHODS: Historical review and summaries of specific measures designed to characterize effort level in assessment of persons suffering TBI. RESULTS: There are several effort level measures that have withstood the scrutiny of cross-validation research. These include the Computerized Assessment of Response Bias (CARB), Portland Digit Recognition Test (PDRT), Test of Memory Malingering (TOMM), Validity Indicator Profile (VIP), Victoria Symptom Validity Test (VSVT), and Word Memory Test (WMT). CONCLUSIONS: Depending on the neurocognitive test performances(s) evidencing suboptimal effort or complaints that may be questionable, it is recommended that at least 2 of the above-listed measures be employed for proper assessment of effort level.

Meyers, J. E. and A. Diep (2000). "Assessment of malingering in chronic pain patients using neuropsychological tests." Appl Neuropsychol **7**(3): 133-139.

Validity checks into neuropsychological tests have been successful at detecting malingering in litigant patients with mild brain injury in recent years. This study expanded on these findings and examined whether 6 neuropsychological tests could be used to detect malingering in litigant (n = 55) and nonlitigant (n = 53) patients claiming cognitive deficits due to chronic pain. Encouraging findings were found. When patients were matched on age, gender, racial or ethnic background, years of education, and time postinjury, almost one third (29%) of patients in the litigant group failed 2 or more validity checks in these 6 neuropsychological tests versus none (0%) of the patients in the nonlitigant group. This result challenges the validity of some litigant patients who complain of cognitive deficits due to chronic pain. Furthermore, the findings suggest that neuropsychological assessments can be used as part of the assessment of chronic pain complainants. Further investigation of the validity markers in these 6 neuropsychological tests is recommended.

Mittenberg, W., et al. (2002). "Base rates of malingering and symptom exaggeration." J Clin Exp Neuropsychol **24**(8): 1094-1102.

Base rates of probable malingering and symptom exaggeration are reported from a survey of the American Board of Clinical Neuropsychology membership. Estimates were based on 33,531 annual cases involved in personal injury, (n = 6,371). disability (n = 3,688), criminal (n = 1,341), or medical (n = 22,131) matters. Base rates did not differ among geographic regions or practice settings, but were related to the proportion of plaintiff versus defense referrals. Reported rates would be 2-4% higher if variance due to referral source was controlled. Twenty-nine percent of personal injury, 30% of disability, 19% of criminal, and 8% of medical cases involved probable malingering and symptom exaggeration. Thirty-nine percent of mild head injury, 35% of fibromyalgia/chronic fatigue, 31% of chronic pain, 27% of neurotoxic, and 22% of electrical injury claims resulted in diagnostic impressions of probable malingering. Diagnosis was supported by multiple sources of evidence, including severity (65% of cases) or pattern (64% of cases) of cognitive impairment that was inconsistent with the condition, scores below empirical cutoffs on forced choice tests (57% of cases), discrepancies among records, self-report, and observed behavior (56%), implausible self-reported symptoms in interview (46%), implausible changes in test scores across repeated examinations (45%), and validity scales on objective personality tests (38% of cases).

Ortega, A., et al. (2013). "Diagnostic accuracy of a bayesian latent group analysis for the detection of malingering-related poor effort." Clin Neuropsychol **27**(6): 1019-1042.

In the last decade, different statistical techniques have been introduced to improve assessment of malingering-related poor effort. In this context, we have recently shown preliminary evidence that a Bayesian latent group model may help to optimize classification accuracy using a simulation research design. In the present study, we conducted two analyses. Firstly, we evaluated how accurately this Bayesian approach can distinguish between participants answering in an honest way (honest response group) and participants feigning cognitive impairment (experimental malingering group). Secondly, we tested the accuracy of our model in the differentiation between patients who had real cognitive deficits (cognitively impaired group) and participants who belonged to the experimental malingering group. All Bayesian analyses were conducted using the raw scores of a visual recognition forced-choice task (2AFC), the Test of Memory Malingering (TOMM, Trial 2), and the Word Memory Test (WMT, primary effort subtests). The first analysis showed 100% accuracy for the Bayesian model in distinguishing participants of both groups with all effort measures. The second analysis showed outstanding overall accuracy of the Bayesian model when estimates were obtained from the 2AFC and the TOMM raw scores. Diagnostic accuracy of the Bayesian model diminished when using the WMT total raw scores. Despite, overall diagnostic accuracy can still be considered excellent. The most plausible explanation for this decrement is the low performance in verbal recognition and fluency tasks of some patients of the cognitively impaired group. Additionally, the Bayesian model provides individual estimates, p(zi |D), of examinees' effort levels. In conclusion, both high classification accuracy levels and Bayesian individual estimates of effort may be very useful for clinicians when assessing for effort in medico-legal settings.

Ortega, A., et al. (2014). "A Bayesian latent group analysis for detecting poor effort in a sample of cognitively impaired patients." J Clin Exp Neuropsychol **36**(6): 659-667.

Using a Bayesian latent group analysis in a simulation design, we recently showed a high diagnostic accuracy when assessing effort in the context of malingered memory deficits. We here further evaluate our Bayesian model in a sample of cognitively impaired patients. The main analysis showed both high sensitivity and specificity, thus corroborating a high diagnostic accuracy of the model. Additional analysis showed variations on effort estimates after changes in malingering base rates. Variations affected sensitivity, but not specificity, which is in line with typical findings in malingering research. These data suggest that Bayesian analyses may complement and improve existing effort measures.

Stewart, J. A., et al. (2017). "Motivation for Psychological Treatment Predicts Favorable Outcomes in Multimodal Interdisciplinary Treatment for Chronic Somatoform Pain." Psychother Psychosom **86**(1): 60-61.

Trippolini, M. A., et al. (2014). "Reliability of clinician rated physical effort determination during functional capacity evaluation in patients with chronic musculoskeletal pain." J Occup Rehabil **24**(2): 361-369.

INTRODUCTION: Functional capacity evaluation (FCE) can be used to make clinical decisions regarding fitness-for-work. During FCE the evaluator attempts to assess the amount of physical effort of the patient. The aim of this study is to analyze the reliability of physical effort determination using observational criteria during FCE. METHODS: Twenty-one raters assessed physical effort in 18 video-recorded FCE tests independently on two occasions, 10 months apart. Physical effort was rated on a categorical four-point physical effort determination scale (PED) based on the Isernhagen criteria, and a dichotomous submaximal effort determination scale (SED). Cohen's Kappa, squared weighted Kappa and % agreement were calculated. RESULTS: Kappa values for intra-rater reliability of PED and SED for all FCE tests were 0.49 and 0.68 respectively. Kappa values for inter-rater reliability of PED for all FCE tests in the first and the second session were 0.51, and 0.72, and for SED Kappa values were 0.68 and 0.77 respectively. The inter-rater reliability of PED ranged from kappa = 0.02 to kappa = 0.99 between FCE tests. Acceptable reliability scores (kappa > 0.60, agreement >/=80 %) for each FCE test were observed in 38 % of scores for PED and 67 % for SED. On average material handling tests had a higher reliability than postural tolerance and ambulatory tests. CONCLUSION: Dichotomous ratings of submaximal effort are more reliable than categorical criteria to determine physical effort in FCE tests. Regular education and training may improve the reliability of observational criteria for effort determination.

Williams, J. M. (2011). "The malingering factor." Arch Clin Neuropsychol **26**(3): 280-285.

The influence of malingering and suboptimal performance on neuropsychological tests has become a major interest of clinical neuropsychologists. Methods to detect malingering have focused on specialized tests or embedded patterns associated with malingering present in the conventional neuropsychology tests. There are two stages to the study of their validity. The first stage involves whether the method can discriminate malingering subjects from those who are not malingering. In the second stage, they must be examined for their relationship to the conventional tests used to establish impairment and disability. Constantinou, Bauer, Ashendorf, Fisher, and McCaffrey (2005. Is poor performance on recognition memory effort measures indicative of generalized poor performance on neuropsychological tests? Archives of Clinical Neuropsychology, 20, 191-198.) conducted the only study in which correlations are presented between a commonly used symptom validity test, the Test of Memory Malingering (TOMM) and the subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R). A factor analysis was conducted using these correlations. It revealed a clear malingering factor that explained significant variance in the TOMM and the WAIS-R subtests. The relationship of malingering with cognitive tests is complex: some tests are sensitive to malingering and others are not. Factor analysis can summarize the magnitude of variance associated with each test and reveal the patterns of inter-relationships between malingering and clinical tests. The analysis also suggested that malingering assessment methods could be improved by the addition of timing the responses.

Appendix 2: PICO Questions

Chronic Persistent Pain and Chronic Pain Syndrome

1. Is there evidence for the use of laboratory tests for chronic persistent pain?
2. Is there evidence to support the use of antibodies to confirm specific disorders?
3. Is there evidence for using ANSAR Testing for diagnosing chronic persistent pain?
4. What evidence exists for using nonspecific inflammatory markers for screening inflammatory disorders?
5. What evidence supports use of cytokine testing for chronic persistent pain?
6. Is there evidence for the use of needle EMG and/or nerve conduction studies to diagnose chronic persistent pain?
7. What evidence supports use of surface EMG when diagnosing chronic persistent pain?
8. Is there evidence supporting use of functional MRIs for diagnosing chronic persistent pain?
9. Is there evidence to support use of local anesthetic injections for diagnosing chronic persistent pain?
10. What is the evidence for the use of SPECT/PET for diagnosing chronic persistent pain?
11. Is there evidence for using FCEs when diagnosing chronic persistent pain?
12. What is the evidence regarding bed rest and chronic persistent pain?
13. Is there evidence to support sleep posture and chronic persistent pain?
14. What evidence supports specialty beds/products and chronic persistent pain?
15. What is the evidence supporting aerobic exercise and chronic persistent pain?
16. What evidence supports strengthening exercise and chronic persistent pain?
17. What evidence supports stretching exercise and chronic persistent pain?
18. What is the evidence for aquatic therapy and chronic persistent pain?
19. Is there evidence for yoga and chronic persistent pain?
20. What is the evidence for physical or occupational therapy for chronic persistent pain?
21. Is there evidence for the use of oral NSAIDs and chronic persistent pain?
22. What evidence exists for the use of acetaminophen and chronic persistent pain?
23. What evidence exists for the use of norepinephrine reuptake inhibitor anti-depressants for chronic persistent pain?
24. Is there evidence for use of selective serotonin reuptake inhibitors (SSRIs) for chronic persistent pain?
25. What is the evidence for duloxetine for chronic persistent pain?
26. What is the evidence for the use of anti-convulsants (except topiramate) for chronic persistent pain?
27. What evidence supports the use of topiramate for chronic persistent pain?
28. What is the evidence to support use of gabapentin or pregabalin for chronic persistent pain?
29. Is there evidence to support the use of clonidine for chronic persistent pain?
30. Is there evidence for the use of epidural clonidine for chronic persistent pain?
31. What is the evidence regarding ketamine infusions and chronic persistent pain?
32. Is there evidence for the use of dextromethorphan and chronic persistent pain?
33. What evidence supports the use of glucocorticosteroids for chronic persistent pain?
34. Is there evidence to use ketanserin for chronic persistent pain?

35. What evidence exists to support the use of muscle relaxants and chronic persistent pain?
36. Is there evidence for the use of topical NSAIDs for chronic persistent pain where there is superficially located target tissue?
37. What evidence exists for the use of EMLA cream and chronic persistent pain?
38. Is there evidence for using lidocaine patches for chronic persistent pain?
39. What is the evidence for tumor necrosis factor-alpha blocker for chronic persistent pain?
40. Is there evidence for the use of magnets or magnetic stimulation for chronic persistent pain?
41. What evidence exists for taping or kinesiotaping for chronic persistent pain?
42. Does evidence support self-application of cryotherapies for chronic persistent pain?
43. What is the evidence to support provider-applied cryotherapies for chronic persistent pain?
44. What is the evidence for self-application of heat therapies for chronic persistent pain?
45. What is the evidence for diathermy for chronic persistent pain?
46. Is there evidence for using external radiation for sympathetic blockade for chronic persistent pain?
47. What evidence supports the use of ultrasound for chronic persistent pain?
48. Is there evidence for provider-based or self-application of infrared therapy for chronic persistent pain?
49. What is the evidence for use of low level laser therapy for chronic persistent pain?
50. Does evidence support the use of manipulation for chronic persistent pain?
51. What is the evidence for massage and chronic persistent pain?
52. Is there evidence for use of mechanical massage devices for chronic persistent pain?
53. Is there evidence for myofascial release for chronic persistent pain?
54. What is the evidence regarding acupuncture and chronic persistent pain?
55. What evidence exists for use of reflexology and chronic persistent pain?
56. Is there evidence supporting the use of high-voltage galvanic therapy for chronic persistent pain?
57. What is the evidence for H-Wave® Device Stimulation for chronic persistent pain?
58. Is there evidence to support the use of interferential therapy for chronic persistent pain?
59. What evidence exists for iontophoresis for chronic persistent pain?
60. Is there evidence to support the use of microcurrent electrical stimulation for chronic persistent pain?
61. What is the evidence for PENS and chronic persistent pain?
62. What is the evidence for TENS and chronic persistent pain?
63. Is there evidence for using intrathecal bupivicaine infusions and chronic persistent pain?
64. What evidence supports lidocaine infusions and chronic persistent pain?
65. Is there supporting evidence for intrathecal drug delivery systems for chronic persistent pain?
66. What is the evidence for psychological evaluation in chronic persistent pain?
67. Is there evidence to support herbal/other preparations for chronic persistent pain?
68. What evidence supports the use of vitamins for chronic persistent pain?

Complex Regional Pain Syndrome

1. Is there evidence for using antibodies for diagnosing chronic pain with a suspicion of a rheumatological disorder?
2. What evidence supports use of antibodies to diagnose a specific rheumatological disorder?

3. Is ANSAR testing recommended to diagnose CRPS?
4. Is Bone Scanning recommended for diagnosing CRPS?
5. What is the evidence for use of non-specific inflammatory markers for screening inflammatory disorders?
6. Is there evidence supporting cytokine testing for diagnosing CRPS and Chronic Pain?
7. Is there evidence supporting Surface EMG for diagnosing CRPS and Chronic Pain?
8. Does the evidence support using Functional EMGs for diagnosing CRPS?
9. Is there evidence for using Local Anesthetics for diagnosing CRPS?
10. What is the evidence to support OSART for diagnosing CRPS?
11. What evidence supports use of SPECT/PET for diagnosing Chronic Pain?
12. Is Thermography recommended for diagnosing Chronic Pain?
13. What is the evidence regarding Bed Rest and CRPS?
14. How does Aerobic Exercise impact CRPS?
15. What is the evidence supporting Strengthening Exercises and CRPS?
16. What evidence exists for Stretching Exercises and CRPS?
17. Is there evidence supporting Mirror Therapy and CRPS?
18. Is there evidence to support Aquatic Therapy for CRPS?
19. What is the evidence regarding Desensitization Techniques and CRPS?
20. What is the evidence regarding Yoga and CRPS?
21. Are Oral NSAIDS effective for CRPS?
22. Is Acetaminophen effective for CRPS?
23. What evidence supports the use of Intravenous NSAIDS for CRPS?
24. Is there evidence for the use of Duloxetine for CRPS?
25. What evidence exists for the use of Selective Serotonin Reuptake Inhibitors (SSRIs) for CRPS?
26. What evidence supports the use of Anti-convulsants for CRPS?
27. Is the short term use of Gabapentin or Pregabalin recommended for CRPS?
28. What evidence exists for the use of Bisphosphonates for CRPS?
29. Is there evidence for the use of Calcitonin for CRPS?
30. Is there evidence to support using Clonidine for CRPS?
31. What is the evidence regarding the use of Intravenous Regional Anesthesia with Clonidine pre CRPS surgery?
32. Are Oral Glucocorticosteroids recommended for CRPS?
33. What is the evidence for the use Intrathecal Glucocorticosteroids for CRPS?
34. Is there evidence for Ketamine Infusion for CRPS?
35. What evidence exists for Ketanserin for CRPS?
36. Is there evidence supporting the use of Magnesium Sulfate for CRPS?
37. What evidence supports the use of NMDA Receptors/Antagonists for CRPS?
38. Is there evidence to support the use of Muscle Relaxants for CRPS?
39. What evidence exists for the use of Thalidomide or Lenalidomide for CRPS?
40. What evidence exists for using Capsicum Cream for CRPS?
41. What is the evidence for the use of DMSO and CRPS?
42. Is there evidence for N-Acetylcysteine (NAC) use for CRPS?
43. What evidence supports EMLA Cream and CRPS?
44. Is there evidence to support using Tumor Necrosis Factor-alpha Blockers for CRPS?

45. Is there evidence for using Intravenous Immunoglobulin (IVIG) for CRPS?
46. What evidence supports the use of Vitamin C for Prevention of CRPS in patients with wrist fractures, extreme trauma or other high risk populations?
47. What evidence supports use of Mannitol for CRPS?
48. What evidence exists for Opioid use in CRPS?
49. Is there evidence for use of Hyperbaric Oxygen in CRPS?
50. Is there evidence for using Magnets or Magnetic Stimulation in CRPS?
51. Is an Occlusal Splint recommended for CRPS?
52. Is Taping or Kinesiotaping recommended for CRPS?
53. What is the evidence for use of Acupuncture in CRPS?
54. What is the evidence surrounding Cryotherapies and CRPS?
55. Is there evidence for the use of Self-Application of Heath Therapy in CRPS?
56. What evidence supports use of Diathermy in CRPS?
57. Is there evidence for use of External Radiation for Sympathetic Blockade for CRPS?
58. What evidence supports Infrared Therapy use in CRPS?
59. Is there evidence for the use of Low Level Laser Therapy for CRPS?
60. What evidence supports Manipulation in CRPS?
61. Is Myofascial Release recommended for CRPS?
62. Is Reflexology recommended for CRPS?
63. What evidence exists regarding High-voltage Galvanic Therapy for CRPS?
64. Is there evidence supporting use of H-Wave® Device Stimulation for CRPS?
65. What evidence exists for Interferential Therapy for CRPS?
66. Is there evidence supporting Iontophoresis for CRPS?
67. What evidence exists regarding Microcurrent Electrical Stimulation for CRPS?
68. Is there evidence to support PENS for CRPS?
69. What evidence exists for the use of Sympathetic Electrotherapy for CRPS?
70. What is the evidence for the use of TENS and CRPS?
71. Is there evidence to support use of Botulinum Toxin Injections for CRPS/
72. What evidence supports Intrathecal Baclofen for CRPS?
73. Is there evidence for the use of Intrapleural Bupivacaine Infusions in CRPS?
74. What evidence supports the use of Lidocaine Infusions in CRPS?
75. What evidence exists for Stellate Ganglion Blocks for CRPS?
76. What evidence exists for Bier Blocks for CRPS?
77. What evidence exists for Guanethidine Bier Blocks for CRPS?
78. What evidence exists for Bretylium Bier Blocks for CRPS?
79. What evidence exists for Phentolamine Bier Blocks for CRPS?
80. What evidence exists for Methylprednisolone Bier Blocks for CRPS?
81. Is there evidence for Reserpine Bier Blocks for CRPS?
82. What is the evidence for the use of Brachial Plexus Blocks and Infusions for CRPS?
83. Is there evidence to support the use of Spinal Cord Stimulators for short to intermediate term relief of CRPS?
84. What is the evidence supporting amputation in CRPS?

Fibromyalgia

1. What is the evidence for the use of Antibodies for diagnosing FM?
2. Is there evidence for the use of Non-specific Inflammatory Markers for diagnosing FM?
3. Is ANSAR testing recommended for diagnosing FM?
4. What evidence is available for using Functional MRIs for diagnosing FM?
5. Is there evidence for the use of SPECT/PET for diagnosing FM?
6. Are Needle EMG and/or Nerve Conduction Studies recommended for diagnosing FM?
7. Is there evidence to support use of Surface EMG for diagnosing FM?
8. What evidence supports use of Local Anesthetic injections for diagnosing FM?
9. Is there evidence for Functional Capacity Evaluations for diagnosing FM?
10. What is the evidence for Bed Rest and FM?
11. What is the evidence for Fear Avoidance Belief Training and FM?
12. What evidence supports Aerobic Exercise for FM?
13. Is there evidence for Strengthening, Stabilization and/or Resistance Exercise for FM?
14. What evidence supports Stretching Exercises for FM?
15. Is there evidence for Yoga and FM?
16. Is there any evidence supporting Pilates for FM?
17. What evidence supports Swimming for FM?
18. Is Aquatic Therapy (Not Swimming) recommended for FM?
19. Is there evidence to support Tai Chi for FM?
20. What is the evidence supporting Spa and Balneotherapy for FM?
21. Is there evidence to support the use of Whole Body Vibration for FM?
22. What evidence exists regarding the use of Oral NSAIDs for FM?
23. Is Acetaminophen recommended for FM?
24. What is the evidence for using Norepinephrine Reuptake Inhibitor Anti-depressant (TCAs) for FM?
25. Is there evidence for the use of Selective Serotonin Reuptake inhibitors (SSRIs) for FM?
26. Is there evidence for the use of Serotonin Norepinephrine Reuptake Inhibitors such as Duloxetine and Milnacipran for FM?
27. What evidence supports the use of Noradrenergic and Specific Serotonergic Antidepressants for FM?
28. Is there evidence for using Serotonin Receptor Antagonists for FM?
29. What is the evidence for use of Bupropion, Trazadone or Pramipexole for FM?
30. Is there evidence for using Atypical Anti-depressants for FM?
31. What evidence exists for the use of NMDA Receptor Antagonists for FM?
32. Is there evidence supporting use of Anti-convulsants for FM?
33. What evidence exists for the use of Glucocorticosteroids for FM?
34. Is there evidence to support the use of Dehydroepianrosterone (DHEA) for FM?
35. Is there evidence supporting the use of Calcitonin for FM?
36. What is the evidence for the use of Vitamin D for FM?
37. Is Melatonin recommended for use in FM?
38. Is there evidence for the use of Hormone Replacement Therapy (HRT) for FM?
39. Is Raloxifen recommended for FM?
40. Is there evidence to support the use of Oxytocin in FM?

41. Is Growth Hormone (GH) recommended for FM?
42. What evidence supports the use of Pyridostigmine for FM?
43. Is there evidence for the use of Ritanserin in FM?
44. What evidence exists for using 5-Adneosylmethionine for FM?
45. Is there evidence for the use of Creatine in FM?
46. What is the evidence for using Terguride in FM?
47. Is there evidence to support the use of Valcyclovir in FM?
48. What evidence supports the use of Sodium Oxybate in FM?
49. Is there evidence for the use of Zolpidem for FM?
50. What is the evidence for Coenzyme Q for FM?
51. Is there evidence for using Acetyl-1-Carnitine for FM?
52. What evidence exists for using Antidiencephalon for FM?
53. Is there evidence to support the use of Dolasetron for FM?
54. Is there evidence for Zopiclone in FM?
55. What is the evidence for Ondansetron for FM?
56. Is there evidence to support the use of Skeletal Muscle Relaxants for FM?
57. Is there evidence for the use of Alpha1-Antitrypsin for FM?
58. What evidence supports the use of Topical Medications and Lidocaine patches for FM?
59. What is the evidence for using Opioids in FM Patients?
60. Is there evidence for the use of Kinesiotaping and Taping in FM Patients?
61. What evidence supports the use of Magnets/Magnetic Stimulation in FM?
62. What I the evidence for Weight Reduction/Weight Management in FM?
63. Is there evidence for use of Dietary Interventions in FM?
64. Is there evidence to support Music Therapy in FM?
65. Is Homeopathy recommended for FM?
66. Is there evidence supporting Herbal, Alternative, Complementary or Other Preparations in FM?
67. Is there evidence for the use of Reiki Therapy in FM?
68. What evidence supports the use of Qigong I FM?
69. Is there evidence for use of Acupuncture in FM?
70. What evidence exists surrounding the use of Manipulation and Mobilization in FM?
71. Is there evidence supporting massage in FM?
72. Is there evidence for Myofascial Release in FM?
73. Is there evidence for Reflexology for FM?
74. Is there evidence to support Hot and/or Cold Therapies for FM?
75. What is the evidence for Hyperbaric Oxygen use in FM?
76. Is there evidence for Interferential or Ultrasound use in FM?
77. What evidence supports the use of Pulsed Electromagnetic Therapy for FM?
78. Is there evidence to support using Microcurrent Cranial Electrical Stimulation for FM?
79. Is there evidence for using Cortical Electrostimulation for FM?
80. What evidence exists for the use of Transcranial Direct Current for FM?
81. What evidence exists for the use of Transcranial Magnetic Stimulation for FM?
82. What evidence supports the use of Low Level Laser Therapy for FM?
83. Is there evidence supporting the use of Transcranial Electrical Nerve Stimulation (TENS) for FM?
84. What evidence exists for Other Electrical Therapies for FM?

85. Is there evidence for the use of Iontophoresis for FM?
86. What is the evidence for using Ganglion Blocks for FM?
87. Are Ketamine Infusions recommended for FM?
88. Are Lidocaine Infusions recommended for FM?
89. What us the evidence for the use of C2 Nerve Stimulation in FM?
90. Is there evidence for the use of Prolotherapy Injections in FM?
91. What is the evidence for Self-Management for FM?
92. What is the evidence for Body/Self-Awareness for FM?
93. Is there evidence for the use of Attention Modification in FM?
94. What is the evidence surrounding the use of Guided imagery in FM?
95. Is there evidence for the use of Mindfulness Intervention in FM?
96. What is the evidence for Acceptance and Commitment Training in FM?
97. Is there evidence to support Psychoeducational Treatment in FM?
98. Is there evidence supporting Written Pain Education and Disclosures in FM?
99. What evidence supports the use of Shared Decision Making in FM?
100. What is the evidence for Psychological Treatment/Behavioral Therapy in FM?
101. Is there evidence for using Rehabilitation for Delayed Recovery in FM?
102. Is there evidence for using Biofeedback in FM?
103. What evidence exists for the use of Relaxation/Meditation Training in FM?
104. Is there evidence for Functional Restoration in FM?
105. What evidence supports Work Conditioning, Work hardening, and Early Intervention Programs in FM?
106. What is the evidence regarding Interdisciplinary Pain Rehabilitation Programs in FM?
107. Is there evidence for Other “Ad Hoc” Functional Restoration Programs in FM?

Neuropathic Pain

1. Is there evidence supporting Laboratory tests for diagnosing Peripheral NP?
2. Is there evidence for Occupational Neurotoxin Exposure Measurements for diagnosing NP?
3. Is there evidence to support Antibody Testing for confirmation of Specific Disorders?
4. Is ANSAR Testing recommended to confirm Specific NP Disorders?
5. Are Non-specific Inflammatory Markers recommended for screening various Inflammatory Disorders?
6. Is Cytokine Testing recommended for diagnosing Chronic NP?
7. What evidence supports the use of Needle EMG and Nerve Conduction Studies to diagnose NP?
8. IS there evidence to support the use of Surface EMG to diagnose Chronic NP?
9. What evidence supports the use of Functional MRIs for diagnosing Chronic NP?
10. Is there evidence to support Local Anesthetic injections for diagnosing Chronic NP?
11. What evidence supports the use of SPECT/PET for diagnosing Chronic NP?
12. Are FCE’s recommended for diagnosing Chronic NP?
13. What is the evidence for Bed Rest and NP?
14. Is there evidence to support Aerobic Exercise for NP?
15. Is there evidence for Strengthening Exercise for NP?
16. What is the evidence for Aquatic therapy and NP?
17. What evidence supports Physical and/or Occupational Therapy for NP?

18. What evidence exists for the use of NSAIDS for Chronic NP?
19. Is there evidence for Acetaminophen for NP?
20. What evidence exists for the use of Tricyclics Tetracyclics and SNRI Anti-depressants for NP?
21. What is the evidence for Selective Serotonin Reuptake inhibitors for NP?
22. Is there evidence for using Antipsychotics for NP?
23. What evidence exists for use of Anti-convulsants for NP?
24. Is there evidence to support the use of Anti-virals for NP?
25. What evidence exists for the use of Homeopathy and Complementary Medicine for NP?
26. Is there evidence for the use of Clonidine for NP?
27. What is the evidence for using Dextromethorphan for NP?
28. Is there evidence for the use of Muscle Relaxants for Acute Exacerbation of NP?
29. What evidence supports the use of Magnesium for NP?
30. Is there evidence to support the use of Tumor Necrosis Factor-alpha Blockers for NP?
31. Is there evidence to support the use of Topical NSAIDs for Chronic NP where the target tissue is superficially located?
32. Is there evidence supporting Other Topical creams such as Ketamine, Amitriptyline and Combinations for NP?
33. What is the evidence surrounding the use of Capsaicin Patches for NP?
34. What evidence exists for using Lidocaine patches for NP?
35. Is Motor Cortex Stimulation recommended for NP?
36. Is there evidence for the use of Magnets or Magnetic Stimulation for NP?
37. What evidence exists for Taping and Kinesiotaping for NP?
38. Is there evidence for Self-application or Healthcare Provider Application of Cryotherapies for NP?
39. What is the evidence for the use of Diathermy for NP?
40. Is there evidence to use Ultrasound for NP?
41. What evidence exists for Provider-Based or Self-Application of Infrared Therapy for NP?
42. Is there evidence to support the use of Low Level Laser Therapy for NP?
43. What is the evidence surrounding Manipulation for NP?
44. Is there evidence for the use of Massage for NP?
45. What evidence supports the use Mechanical Massage Devices for NP?
46. Is there evidence for Myofascial Release for NP?
47. What is the evidence for Acupuncture/Electroacupuncture for NP?
48. Is there evidence to use Reflexology for NP?
49. Is there evidence for the use of High-voltage Galvanic Therapy for NP?
50. What evidence exists for H-Wave® Device Stimulation for NP?
51. Is there evidence for the use of Interferential Therapy for NP?
52. Is there evidence for Iontophoresis for NP?
53. What is the evidence for the use of Microcurrent Electrical Stimulation for NP?
54. Is there evidence to support the use of PENS for NP?
55. Is there evidence to support the use of TENS for NP?
56. What evidence exists regarding Repetitive Transcranial Magnetic Stimulation (rTMS) and NP?
57. What evidence exists for the use of Sympathetic Electrotherapy and NP?
58. Is there evidence for the use of External Radiation for Sympathetic Blockade for NP?

59. What evidence supports the use of Corticosteroids for NP?
60. Is there evidence for the use of Immunoglobulin for NP?
61. What evidence supports using Ketamine Infusions for NP?
62. Is there evidence to use Intrapleural Bupivacaine Infusions for NP?
63. Is there evidence supporting the use of Lidocaine Infusions for NP?
64. What is the evidence regarding Intravenous Phenytoin for NP?
65. What is the evidence regarding Intravenous Adenosine for NP?
66. Is there evidence to support the use of Monoclonal Antibody Injections for NP?
67. Is there evidence regarding Dorsal Ganglion Destruction for NP?
68. What evidence exists for Nerve Blocks and NP?
69. Is there evidence for Surgical Decompression for NP?
70. What is the evidence for Spinal Cord Stimulation for NP?
71. Is there evidence for Intrathecal Drug Delivery Systems for Chronic Nonmalignant NP?

Chronic Pain Rehabilitation

1. What is the evidence regarding Work Conditioning, Work Hardening, Early Interventional Programs and Back Schools for Chronic Pain?
2. Is there evidence to support Tertiary Pain Programs, Interdisciplinary Pain Rehabilitation Programs, Multidisciplinary Pain Programs, Chronic Pain Management Programs or Functional restoration programs for Chronic Pain?
3. Is there evidence for participatory Ergonomics Programs for Chronic Pain Patients?

Behavioral Chronic Pain

1. What evidence suggest Psychological Evaluation for Chronic Pain Patients?
2. Is there evidence to support Cognitive Behavioral Therapy for Chronic Pain Patients?
3. What is the evidence supporting Fear Avoidance Belief Training for Chronic Pain Patients?
4. Is there evidence for use of Biofeedback in Chronic Pain Patients?

APPENDIX 3: Interval Pain History

What do you hope to accomplish during this visit?

What are your concerns about the potential for further injury as you recover?

What are your expectations regarding your return to work and disability from this health problem?

What are your symptoms since we last talked?

- Where are the symptoms located?
- How bad is the pain, (e.g., on a 0 to 10 scale)?
- Do you have pain or stiffness?
- Do you have numbness or tingling?
- Do you have pain or other symptoms elsewhere?
- Have you lost control of your bowel or bladder?
- Do you have fever, night sweats, or weight loss?
- Are your symptoms constant or intermittent?
- What makes the problem worse or better?
- What is the day pattern to your pain?
- Better first getting out of bed in the morning, during the morning, mid-day, evening or while asleep?
- When is it worst?
- Do you have a problem sleeping?
- What position is most comfortable?
- Is there any pain with cough, sneezing, deep breathing, or laughing?
- Since these symptoms began, have your symptoms changed? How?
- How does having this pain affect your life?

Job

- Are you working at your regular job?
- How long do you spend performing each duty on a daily basis?
- What tasks are you doing on your modified or light job?
- Do you have assistance from other people or lifting devices?
- Are you on modified or light duty?
- What are your work hours and breaks?
- Do you rotate jobs?
- What is the hardest part of the job for you to do with your injury? Why?
- How much do you lift at work as a maximum? Usual lift?
- How often do you do those tasks?
- Describe work times, movement and breaks for sedentary jobs

Off-work Activities:

- What other activities (hobbies, workouts, sports) do you engage in, at home or elsewhere?

- Describe your current daily activities starting with waking up to bedtime.
- Do you go grocery shopping, prepare your own meals, do yard work and laundry?
- Family, sexual function
- How heavy?
- Lifting from what height?
- How large is(are) the objects?
- How often?
- Do you carry objects long distances?
- Do you sit for long periods of time?
- Any heavy or difficult lifting?

Interval Treatments and Activities

- What treatments and medications have you received (include complete medication review)?
- Did treatment help decrease your symptoms?
- What and for how long?
- Did it help?
- How?
- How often do you perform them? When?
- Do you feel that they help?
- Show me how you do them.
- Exactly what treatment did you receive or participate in physical therapy (detailed descriptions of all modalities and specific exercises used)?
- Are you doing physical therapy exercises at home?

Symptom Limitations

- How do these symptoms limit you?
- How long can you sit, stand, walk, and bend?
- Can you lift?
- How much weight (use items such as gallons of milk, groceries, etc. as examples)?
- How much can you push or pull?
- Do you need to lie down or rest during the day?
- What activities at home do you need help with?
- What activities do you perform in a typical day? Begin with waking in the morning and proceed to bedtime.
- What activities are you now unable to do? Why?

Is there any change in medical conditions, psychological, psychiatric, mental health, substance use, alcohol or tobacco disorder history?

What is the occupational psychosocial context?

- If you had to take a job again, would you go back to your current job?
- Do you like your job at this point?
- What is your relationship with your co-workers and supervisor and how do they treat you now?
- How do you get along with your supervisor now?

- How do you get along with your coworkers now?
- How do your coworkers help you if you need it at this point?
- How does your supervisor help you if you need help now?
- Is your employer concerned about you now?
- Are you facing any disciplinary or performance action now?

Assess whether there are problems at home/social life. Does the patient feel in control of most situations? Is there support?

- How do your family members get along with each other now?
- How do they help and support you now?
- Does your family treat you differently now?
- Have your roles at home changed because of your injury?
- How do your friends treat you differently?
- Do you get increased symptoms when you are dealing with problems with your family and friends? How often? When? Why?

Are There Advocagenic (Litigious) Influences?

- Do you have a workers' compensation claim for this injury?
- Do you a lawsuit or other legal action involving this pain problem?
- Have you consulted anyone (union representative, etc.) about particular problems you may have experienced with your claim (not receiving benefits, etc.)?
- Do you have additional insurance coverages such as short- or long-term disability?
- Have you taken sick time for this problem?
- Did you talk with your lawyer about what you should say at the clinic?
- Do you have a lawyer? Have you ever been involved in a lawsuit?

Appendix 4. Systematic and Non-systematic Reviews, Low-quality RCTs, and Non-randomized Studies

The following reviews, low-quality randomized controlled studies (RCTs), and other studies and guidelines, were reviewed by the Evidence-based Practice Chronic Pain Panel to be all inclusive, but were not relied upon for purposes of the development of this document's guidance on treatments because they were not of high quality due to one or more errors (e.g., lack of defined methodology, incomplete database searches, selective use of the studies and inadequate or incorrect interpretation of the studies' results, etc.), which may render the conclusions invalid. ACOEM's Methodology requires that only moderate- to high-quality literature be used in making recommendations.

Chronic Pain

ACTIVITY MODIFICATION AND EXERCISE

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Omer 2003 RCT	2.0	N = 50 with cumulative trauma disorder (CTD)	Training course: educational program only (n = 25) vs. training course followed by mobilization and stretching, strengthening, and relaxation exercises 5 days a week for 2 months. Both groups received a 1-hour educational program.	Post-treatment NRS: study group (1.52±2.18) vs. control (5.68±1.79), p <0.001. Post-treatment PDI: study (8.16±12.91) vs. control (16.68±12.42), p <0.05. Post-treatment BECK: study (8.52±5.90) vs. control (12.08±8.20), p<0.05. Post-treatment TS: NS between groups.	"Mobilization, stretching, strengthening and relaxation exercises reduce pain and depression levels of CTD patients in the short term."	Interventions not well described; patients had multiple potential diagnoses, also not well described. Some differences in baseline data appear to favor intervention group. Use of training group only for a control group may result in a biased study design in favor of intervention.

Esenyel 2007 RCT	1.5	N = 90 with chronic myofascial pain in 1 side of upper trapezius muscle of 6 months duration	Botulinum toxin A injections 10U (group 1, n = 18) vs. lidocaine 0.5% 1mL (group 2, n = 18) vs. conventional ultrasound (group 3, n = 18) vs. high-power pain threshold ultrasound (group 4, n = 18) vs. stretching exercise (group 5, n = 18).	At 1 month post-treatment, statistically significant improvements detected in both Lidocaine Trp and Botox A Trp injection groups when compared to other groups, p <0.05. No statistically significant difference found between lidocaine and Botox A injection groups.	"Lidocaine and Botox A Trp injections were more effective in treating patients with chronic MPS in one month controls. Both techniques in US treatment were equally effective."	Processes used in ultrasound arms would unblind group, particularly pain threshold group. Number of trigger points treated unclear. Table referenced in text does not match description of subjects' ages, and comment that there were no statistically significant differences between groups at baseline.

Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Acetaminophen

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Adams 2006 RCT	2.5	N = 11,352 with non-malignant chronic pain for at least 4 months	NSAIDs (n = 4,039) vs. Tramadol (n = 1,517), Tramadol (n = 1,475), Hydrocodone (n = 3,145) vs. Tramadol (n = 1,176). Follow-up at baseline, 2 weeks, 1, 2, 3, 4, 6, 9, and 12 months.	Hydrocodone favored over NSAIDs and tramadol (p <0.01). Abuse of hydrocodone significantly higher than tramadol or NSAIDs (p <0.01).	"These results support the hypothesis that the rate of abuse identified with tramadol is not significantly greater than NSAIDs, but is less than the rate associated with hydrocodone."	Study does not have demonstrated changes in outcomes measures such as RTW.

Anti-depressants

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Ward 1984. 1986	3.0	N = 36 with chronic pain for at least 6 months	Treatment started with 2 weeks of placebo. Those responding to	Doxepin reduced pain severity	"[T]he antidepressants have been misnamed. They are capable of treating a variety of nondepressive conditions	Six continued in study on fixed doses of opiate-related

RCT		diagnosed as having a major affective disorder, unipolar depression, or dysthymic disorder	placebo dropped. Doxepin 50mg vs Desipramine 50mg. Treatments for 4 weeks; target doses 3mg/kg. Average final doses: doxepin 188mg, desipramine 173mg. Follow-up weekly until 6th week.	significantly more than desipramine.	that can be linked by our chronic distress/learned helplessness model." Second study found "[D]esipramine was as effective as doxepin with 60% of patients having significant pain relief. "Pain relief was associated with depression relief, but several patients had only pain or depression relief."	medications and 5 of 6 responded positively to treatment.

Calcitonin

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Gobelet 1986 RCT	3.5	N = 24 with Stage 1 RSDS following trauma affecting extremities	Group 1: intermittent positive pressure treatment, pulsed high frequency analgesic electrotherapy, active mobilization, 5 times weekly for 3 weeks, then 3 times weekly to Week 8 (n = 12) vs. same PT as before with 1 ampoule of 100 units salmon calcitonin daily by injection first 3 weeks (n = 12); follow-up for up to 8 weeks.	Group 2 favored in reduction of pain at 1 week. Four of 12 (33%) from PT alone group vs. 6 of 12 (50%) from PT with calcitonin group fit for work at 8 weeks; 19 of 24 fit for work at 24 weeks.	"[I]t seems that the addition of salmon calcitonin to treatment by physical therapy provides more rapid pain relief in RSDS. This effect seems to us to be of some importance, since it permits active mobilization at an earlier stage and consequently improves the chances of complete functional recover in patients affected by RSDS."	Data suggest PT plus calcitonin superior to PT alone.

Hamamci 1996 RCT	3.5	N = 41 in Turkey with chronic RSD of approximately 2 years duration that developed in hemiplegics from cerebrovascular events	Intervention group (n = 25) received salmon calcitonin, 1x100 IU a day intramuscularly for 4 weeks. Control group (n = 16) received physiological saline, 1ml a day intramuscularly for 4 weeks with follow-ups for 4 weeks.	At 4 weeks pain score of calcitonin group favored over control group (p <0.001). Calcitonin favored in reduction of tenderness (p = 0.003). ROM improved in calcitonin group to greater extent (e.g., shoulder flexion from 112º to 151º in calcitonin vs. from 96º to 113º in placebo).	"[A]t the end of the fourth week of treatment, the pain score of the calcitonin group was significantly lower than that of the control group. Shoulder abduction and external rotation, wrist flexion and metacarpophalangeal extension of the calcitonin group were found to be significantly better than those of the control group. In the calcitonin group the significant decrease in pain and tenderness resulted in improvement of range of motion and motor functions."	Study design unclear as randomization not described, but was placebo controlled.

Ketanserin

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Hanna 1989 RCT	3.5	N = 16 with severe peripheral burning pain	Separated based on signs of RSD or non-RSD, then randomly placed in Group X (n = 6) which received 2 ketanserin treatments followed by 2 placebo treatments vs. Y (n = 10) 2 placebo treatments followed by 2 ketanserin treatments. Treatments weekly, placebo and ketanserin buffered to pH 4 and made up to 30mL with isotonic saline. Ketanserin treatments of	For RSD group, significant decrease in main pain score seen in active treatment weeks (p <0.05). For non-treatment limb, increase in temperature significantly greater than that occurring	"[I]n those patients with RSD, ketanserin and not placebo provided significant (p <0.05) sustained pain relief."	Blinding not well described. Small sample size. Data suggest improvement with ketanserin.

			10mg for arm, 20mg for leg pain. Follow-up weekly for 4 weeks.	following placebo ($p < 0.05$).		

Skeletal Muscle Relaxants

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Valtonen 1975 RCT	3.5	N = 400 with painful muscle spasm from 5 spine-related disorders	Placebo (1 tablet 3 times a day) vs. Chlormezanone (1 tablet 200mg 3 times a day) vs. Orphenadrine citrate (1 tablet 100mg 2 times a day) vs. Orphenadrine citrate (35mg plus paracetamol 450mg, 1 tablet 3 times a day) for 100 patients in each group.	No significant difference chlormezanone vs. placebo. Orphenadrine/paracetamol significantly better than placebo ($p < 0.01$) where as orphenadrine just failed to reach significance against placebo ($p < 0.05$). Percent moderate and good effect at 1 week: 53% placebo, 57% chlormezanone, 66% orphenadrine, 71% orphenadrine/paracetamol.	"The superiority of orphenadrine/paracetamol in this study is remarkable because it was achieved with half the recommended dose. Had the full dosage been used, the results might have been appreciably better."	Heterogeneous patient population. Large sample size. Many details sparse. Follow-up time unclear.

Pipino 1991 RCT	2.0	N = 120 with chronic LBP	Pridinol mesilate (n = 60) vs. thiocolchicoside (n = 60) 1 intramuscular injection (4mg) of either treatment, twice daily first 3 days, followed by 1 tablet 2mg pridinol or 2 capsules 4mg thiocolchicoside twice daily orally at meals 4 consecutive days. Follow-ups at baseline and 4/7 days.	No significant differences found between two groups.	"[T]he use of pridinol mesilate in musculoskeletal disorders characterised by muscular contracture is justified on the grounds of its pharmacodynamic effect and general, local and biological safety and tolerability."	Tables and graphs representing distance walked and ROM suggest substantial baseline differences. Combining lack of discussion of randomization suggests this is either not an RCT or was a randomization failure.

DMSO

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Geertzen 1994 RCT	1.5	N = 26 with RSD	Group A: dimethylsulfoxide (50% in water 4 times a day for 3 weeks) (n = 3) vs. Group B RIS block twice a week for 3 weeks (n = 13) with follow-up before treatment and 1, 2, 3, 5, 7, 9 weeks.	Tendency towards better outcome in DMSO group after 7 and 9 weeks.	"[A] multidisciplinary approach consisting of medical and psychological therapy (stress management training) eventually completed with physiotherapy and occupational therapy needed."	As only 3 patients in DMSO group, no robust conclusions possible.

Acupuncture

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Wang 2007 RCT	3.5	N = 72 with cervical myofascial pain syndrome (CMP) in China	Mini-scalpel needle (MSN) (n = 32) vs. trigger point injection (TPI) (n = 32) with follow-ups at 0/2 weeks and 2/3 months.	VAS in MSN significantly improved in all time points, but in TPI only at T1 (p <0.05). MSN only group to improve with trigger points (p <0.001). Pain scores decreased over time in MSN group, falling to approximately 50% of baseline VAS scores, while TPI group improved at 2 weeks, then returned to prior baseline pain scores.	"[T]he effect of the MSN for CMPs is superior to that of the 0.25% lidocaine TP injection."	Trial uses more interventional technique than acupuncture. Higher quality studies are required to evaluate efficacy as well as safety of this procedure.
DiLorenzo 2004 RCT	3.5	N = 101 with hemiparetic shoulder pain syndrome from stroke or head trauma; 3 weeks prior PT required	Standard rehab plus deep dry needling at 4 sites every 5-7 days. Needles left for 5 minutes (n = 54) vs. standard rehab treatment (n = 47). Last follow-up 21 days after treatment.	Dry needling group favored for significant improvement at Day 1 and end of treatment. Excellent pain relief seen more in needling group 59.94% compared to standard rehab 37.7 %.	"[D]ry needling is an effective method to treat TrPs. When used early in the treatment of shoulder pain syndrome among CVA survivors, it exhibits a widely recognised antalgic action."	Magnitude of difference is not large. Application of this study on hemiparetic shoulder pain to occupational disorder(s) is questionable.

He 2005 RCT	3.0	N = 24 female office workers with neck or shoulder pain	Intensive acupuncture plus acupressure to traditional Chinese acupuncture points (16 body and 6 ear acupuncture points) including real acupuncture or electrostimulation (n = 14) vs. sham points (n = 10). All received total of 10 treatments, 3 a week for 3-4 weeks with last follow-up at 3 years.	Quality of sleep test favored treatment group after 9th treatment ($p < 0.01$) and at 2 follow-ups ($p < 0.03$). At 3 year follow-up, pain significantly lower in treatment group ($p = 0.04$). Pain-related activity impairment at home also favored treatment group after 3 years ($p = 0.03$).	"[I]ntensive acupuncture treatment may improve activity at work and several relevant social and psychological variables for women with chronic pain in the neck and shoulders. The effect may last for at least three years."	Electrostimulation discussed in methods section (but not in abstract), thus interventions unclear. Controls received sham electrostimulation through pads, and apparently needle insertions at sites not traditionally acupuncture. Methodological details sparse, including lack of description of potential subject blinding.
Ilbuldu 2004 RCT	2.5	N = 60 with trigger points in upper trapezius muscles	Four weeks sham laser therapy (n = 20) vs. dry needling (n = 20) vs. helium-neon laser therapy (632.8 nm) (n = 20). Follow-up before/after treatment and at 6 months.	VAS at rest ($p<0.05$), VAS at activity ($p < 0.001$), increase of ROM favored laser group compared to dry needling and placebo groups, but these differences lost at 6 month follow-up.	"Laser therapy is effective as a treatment modality in myofascial pain syndrome because of its proven effectiveness, in addition to its noninvasiveness, ease and short-term application."	Successfulness of blinding to sham laser questionable. Lack of benefit at 6-months raises additional questions about utility of laser therapy. Baseline differences include an average of 57.8% more analgesic in dry needling group vs. active laser group, although VAS scores did not similarly reflect that difference.

Ceccherelli 2002 RCT	1.5	N = 42 with shoulder myofascial pain	Needle in skin at depth of 2mm (n = 21) vs. needle deep (1.5cm) into muscular tissue (n = 21); 8 cycles of treatment, first 4 twice a week; last 4 weekly with follow-up before/ after treatment and 1 and 3 months.	Shallow acupuncture group showed a reduction of pain of 38.49% while the deep acupuncture group showed 86.38%. The total score favored the deep acupuncture group at all follow ups after treatment ($p < 0.05$).	"A statistically significant difference rose between the two needling techniques at the end of the treatment and at the follow up after one and three months. Deep acupuncture shows to be better at all times . . ."	Significant baseline differences, particularly in gender, with unclear implications.
Berlin 1989 RCT	1.0	N = 120 with long-term chronic pain syndromes	Psychosomatic correlations in chronic pain patients using electroacupuncture.	Reduction of pain and equalization of amplitudes of pulse of arteria radialis dextra and sinistra is higher in anxious patients.	"The present study shows a better analgesic effect of electroacupuncture in patients with a higher level of anxiety."	Two or more study treatments not described. Very sparse details.

Massage

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Walach 2003 RCT	3.0	N = 29 with chronic non-inflammatory rheumatic pain (duration >6 months)	Massage (n = 19) vs. standard medical care (n = 10) at 3 measurements: pre-treatment, post-treatment, and 3 months follow-up.	ANOVA showed difference in pain between groups (p = 0.001) and a change over time (p <0.05).	"[M]assage can be at least as effective as standard medical care in chronic pain syndromes."	Abstract notes "Because of political and organizational problems, only 29 patients were randomized…" Impacts of these issues unclear and statement seems to allude to high dropout rate among those in standard care. Does not demonstrate efficacy of massage; may have been underpowered. Marked differences in baseline data prohibits strong conclusions, demonstrates methodological flaw.
Plews-Ogan 2005 RCT	3.0	N = 30 adults with chronic musculoskeletal pain (>3 months duration)	Mindfulness-based stress reduction (MBSR) weekly for eight 2½ hour sessions vs. 1 hour massage with standard care given once per week for 8 weeks.	No pain differences between groups at baseline. At 8-week follow-up, massage had pain score of 2.9±2.9 vs. 0.13±2.4 in standard care; p <0.05.	"Mindfulness-based stress reduction may be more effective and longer-lasting for mood improvement while massage may be more effective for reducing pain."	Study details do not include stratified baseline data. Trends in data are somewhat unclear with no uniform pattern between groups.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Mannheimer 1978 RCT	3.0	N = 19 with RA	TENS proximal to wrist: electrodes proximal to wrist (Group I) vs. TENS with lower stimulation: electrodes in same positions, but intensity lower (Group II) vs. TENS over back, electrodes on spine (Group III); 5 minute sessions for 15 days.	Times for holding an object increased with TENS among 94.7% of group I participants vs. 73.7% in Group II and 5.3% of Group III.	"[I]t seems quite clear that TNS is effective in reducing joint pain. The duration of pain relief is longer than has been observed in other painful conditions, such as lumbago, tumours, etc., that have been treated with TNS."	Randomization and other basic methodological considerations not described. Fact that those with TENS over spine reported worse results does not prove TENS works, as plausibility at issue.
Lundeberg 1984 RCT	2.5	N = 60 with multiple disorders including epicondylitis (n = 18), tendinitis (n = 12), LBP (n = 19), FM (n = 6)	Vibratory stimulation at 20 Hz during vs. high frequency TENS vs. placebo TENS vs. 100 Hz vibratory stimulation vs. low frequency TENS vs. 200 Hz vibration vs. 1g aspirin 2 treatments per week with 2-4 days in between for 3 weeks.	No significant differences between groups.	"The present study confirms earlier observations and in addition shows that vibration in patients with myofascial and musculoskeletal pain is more efficient than aspirin and in general as effective as TENS."	Key study details absent and strong conclusions are not tenable.

Lidocaine Infusions

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Lidocaine Infusions						
Yokoyama 2002 RCT	3.5	N = 12 with intractable pain ≥1 year with ≥70 intensity on VAS at rest	IV infusion with 300mg of lidocaine (IV-lido, n = 6) vs. total spinal anesthesia with 20ml of 1.5% lidocaine infused in the operating room (TSA-Lido, n = 6) at 30 day intervals.	At hour 2, significant decrease in VAS for TSA-Lido when compared to IV-lido, p <0.01.	"[I]V lidocaine was not effective while TSA was associated with intractable pain-relief for a week. However, pain relief was not sustained at 30 days."	Small sample size. Diverse population of patients. Data suggest no sustained efficacy.
Petersen 1986 RCT	3.5	N = 18 with chronic pain	Nine had intravenous infusion of 60ml isotone saline or 200mg lidocaine over 30-minute interval. Nine received 5mg lidocaine/ kg body weight in 50ml isotonic saline intravenously or same volume isotonic saline.	Mean duration of an effect was 8 days.	"[I]ntravenous lidocaine may have even long-lasting analgesic effect on both centrally and peripherally originated pain states… the mechanisms of the pain relieving ability of lidocaine as used is unknown."	Sparse results and methods.

Regional Sympathetic Blocks (includes Stellate Ganglion Blocks)

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Bonelli 1983 RCT	3.5	N = 19 with RSD and clinical signs of either limited motion, trophic changes, vasomotor disturbances, edema, or allodynia	Stellate ganglion blocks (stellate ganglion blocks plus 0.5% bupivacaine 15ml every other day for a total of 8 blocks, n = 10) vs. regional intravenous guanethidine blocks (treatment every 4 days, n = 9) for the duration of 16 days. Final follow-up at 3 months.	Differences in pain score between groups at baseline vs. 15 minutes/60/24 hours/48, 15 minutes vs. 60/24/48, and 60 minutes vs. 24/48. Differences in skin temperature at baseline vs. 15 minutes/60/24 hours/48, and 15 minutes vs. 60/24/48. At 3-month follow-up, significant improvement in subjects with Allodynia in regional intravenous guanethidine blocks group: n = 8, p <0.05.	"[I]ntravenous guanethidine, using the method introduced by Bier in 1908, is a good choice in comparison with the results obtained with conventional stellate ganglion block, especially for the prolonged sympathetic blockade and for the smaller number of therapeutic performances and negligible risks and contraindications."	Baseline differences marked and may favor guanethidine. Randomization method not discussed; baseline data suggest randomization failure, which likely eliminates utility of results. Thus, this may not be an RCT. Graphic data presented also suggests groups largely tracked each other throughout 16 day observation period, suggesting no meaningful differences between them.

Psychological treatment/behavioral therapy

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Strong 1998 RCT	3.5	N = 30 with chronic LBP	Psycho-educational treatment: existing hospital program plus 8-hour psycho-educational program (n = 15) vs. control group: existing hospital program plus 8-hour non-specific program which included health education video (n = 15); 3 month follow-up.	Pre- to post-treatment: depressed and negative cognitions (treatment group: pre = -0.33±.792, post = -.355±, control group: pre = .304 ± .738, post = .633±.762, $F(23,1) = 4.77$, $p < 0.04$). No other variables significantly different between groups.	"The results from this study indicate that participation in an 8-hour psychoeducational program resulted in a significant reduction in the patient's level of degressed and negative cognition. This result was found despite the small sample size of the two groups."	Sparse description of methodological details. Unclear follow-up duration.
Turner 1988 RCT	3.5	N = 81 with chronic LBP	Operant behavioral (OB) and cognitive-behavioral (CB) therapy with waiting-list control condition.	Operant behavioral (OB) included aerobic exercises and operant conditioning, participation of spouses; 2 hours/week, 8 weeks (n = 30). Cognitive-behavioral (CB) included systematic progressive muscle relaxation and imagery; 2 hours/ Week, 8 weeks (n = 26).	"The operant behavioral condition appeared to be more effective than the waiting list and the cognitive-behavioral conditions at posttreatment; however, the two treatments were equivalent at the 12-month follow-up."	Patients not well described. Data suggest lack of difference.

				Reference treatment (R) included waiting list control group (n = 25).		
Corey 1996 RCT	3.5	N = 200 with work-related soft tissue injury and no neurological involvement or disability	Limited functional restoration program: exercise, work conditioning, group education, behavioral counseling (FRP, n = 100) vs. usual care: recommendations for limiting narcotic use and encouraging activity despite pain (n = 100) for 35 days maximum.	At follow-up, 100% of FRP group reported back to work vs. 62.5% from Usual Care group (p = 0.02). FRP group reported less pain (5.3±2.90 vs. 6.5±2.24, t = -2.70 p = 0.008). and better sleep than Usual Care (.72 vs .38, t = 3.18, p = 0.002).	"The results of the present study provide support for the efficacy of a limited functional restoration program in reducing subjective pain levels and enhancing return-to-work rates for WCB claimants with chronic pain, particularly with low back pain."	Data suggest better outcomes compared to usual care.
van den Hout 2003 RCT	3.0	N = 84 with LBP for at least 6 weeks, on sick leave with LBP for no more than 20 weeks, and no more than 120 days of sick leaving in past year	Graded activity plus problem solving therapy (n = 45, GAPS) vs. Graded Activity plus group therapy (n = 39, GAGE)	Baseline: Treatment Creditability (GAPS: 6.9±2.0, GAGE: 8.0±1.1, p <0.01), RDQ (GAPS: [0-8] = 20, [9-16] = 40, [17-24] = 40; GAGE: [0-8] = 12.8, [9-16] = 66.7, [17-24] = 20.5; p = 0.05). At 6 and 12 months: nothing significant	"In conclusion, PST turned out to be an effective treatment in LBP. It showed favorable effects in the course of sick leave in the year after the intervention. The intervention may alter the course of work disability and even protect employees against new episodes of sick leave. A logical continuation of the present study would be to examine cost-effectiveness and to explore possibilities for implementation of	Non-significantly lower lost workdays among problem-solving therapy group and fewer failures to return to work (7% vs. 19%), although concerns about success of baseline randomization which mostly favor problem-solving group.

					problem-solving techniques in occupational health care."	
Flor 1993 RCT	2.5	N = 57 with CBP and 21 with chronic TMPDS	Electromyographic biofeedback: EMG-BFB from pain site. Told about stress-tension-pain relationship, but no relaxation instructions (BFB group) vs. cognitive-behavioral therapy: instruction in pain and stress management (CBT group) vs. conservative treatment: best present medical intervention (MED group). Psychological treatments 8 60-minute sessions.	Pre- to post-treatment: BFB group (pre: 3.424±1.085, post: 1.848±1.027) had more significant change in MPI Pain Intensity Scale vs. MED group (Pre: 3.524±1.133, Post: 2.524±1.500) ($p < 0.05$). BFB had significantly PRSS catastrophizing than other two groups. At 2-year follow-up: BFB (1.833±1.154) had significant difference in pain severity vs. MED (2.812±1.174) ($p < 0.05$). BFB (1.195±1.046) also significantly lower.	"Results suggest that pain patients who suffer from musculoskeletal pain problems and display few physical disabilities may profit the most from short-term EMG biofeedback treatment."	Study does not note location of back pain and considering it is mixed with TMJ pain suggests it may have been thoracic-trapezius pain. Dropout rates 40%.
McCauley 1983 RCT	2.5	N = 17 who exhibited CLBP for at least 6 months	Relaxation (n = 8) 8 50-minute individual sessions. vs. self hypnosis (n = 9) 8 50-minute self hypnosis sessions.	No statistical significance between groups.	"While both treatments were effective, neither proved superior to the other."	Small sample size is particularly limiting and precludes significant conclusions. Dropouts and compliance also noteworthy issues.

Basler 1997 RCT	2.5	N = 94 with chronic LBP	Cognitive behavioral treatment and medical treatment vs. control with medical treatment only for 12 weekly 2.5 hour sessions; 6 month follow-up. All received various medical treatments including pain medication, nerve blocks, TENS, PT.	No significant between-group differences.	"A treatment package of cognitive-behavioral and medical procedures is more effective than medical treatment alone. Effects are not pronounced in control over pain, improvement of coping strategies, and reduction of disability scores."	Dropout rates concerning and baseline differences may have consequently occurred. Number of patients per group not identified.
Turner 1982 RCT	2.0	N = 36 with LBP for at least 6 months	Waiting List/Attention Condition (WL, n = 9) vs. Progressive Relaxation Training (PRT, n = 14) vs. Cognitive Behavioral Therapy (CBT, n = 13).	Pre- to post-treatment: PRT vs. CBT: Ability to Tolerate Pain (PRT: 2.9±0.6; CBT: 3.5±0.6, p <0.05), Participation in Activities (PRT: 2.5±0.7; CBT: 3.1±0.8, p <0.05), Average Achievement Toward Five Goals (PRT: 2.5±0.7; CBT: 3.1±0.8, p <0.05), Highest Achievement of Any Goal (PRT: 25.0± 18.0, CBT: 40.0±16.0, p <0.05).	"At the end of treatment, cognitive-behavioral patients did not differ significantly from the relaxation-training group in pain-related behavioral and psychosocial impairment, average pain intensity, or depression. However, cognitive-behavioral-therapy patients felt they were better able to tolerate their pain and participate in normal activities."	Reported baseline variables show substantial differences and appear to be against wait-listed group who had worse severity measures. Two active treatment groups also do not appear particularly comparable.

Bru 1994 RCT	1.0	N = 109 with relatively severe pain in neck, shoulders, and/or back	Cognitive behavior therapy (n = 19) vs. relaxation therapy (n = 15) vs. combined therapy (n = 24) vs. control (n = 53).	Pre to Post 1: cognitive and combined showed significant reduction in intensity of neck pain; relaxation group remained unchanged. Relaxation group had significant change in intensity of LBP. All groups had significant change in intensity of shoulder pain. Only cognitive and combined showed significant change in duration of neck pain; only combined showed significant change in duration of shoulder pain. Likewise, only relaxation showed any significant change in duration of back pain.	"The Cognitive and Combined intervention procedures were the more effective in reducing neck pain, whereas Relaxation was relatively successful in reducing low back. For shoulder pain, however, all three interventions were effective in reducing intensity of pain, whereas only the Cognitive approach to intervention was significantly effective in reducing duration of shoulder pain."	Minimal population description. Heterogeneous disorders. Many details sparse.

Biofeedback

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Biofeedback						
Ryan 2004 RCT	3.5	N = 70 with irritable bowel syndrome, fibromyalgia/ chronic fatigue syndrome, myofascial pain, anxiety with somatic features, or non-cardiac chest pain	Treatment group (biofeedback, progressive relaxation training, breathing retraining, relaxation training, and problem solving, n = 40) vs. control (n = 30) for 8 weeks. Final follow-up at 6 months.	Differences in symptom reduction significant in treatment group from Week 1-8, p <0.05. Costs for all tests associated with referral diagnosis significantly lower in treatment group, p = 0.012.	"Biofeedback based interventions for "functional" disorders can be easily integrated into primary care settings, can reduce symptoms, and may be able to reduce overall medical costs in this group of patients known as heavy utilizers."	Dropouts high.
Spence 1995 RCT	3.5	N = 48 with chronic pain with a history of upper limb pain >10 months.	EMG biofeedback (n =12) vs. relaxation training (n = 12) vs. combination (n = 12) vs. wait-listed controls (n = 12). Each treatment given 2 times a week for 4 weeks. Final follow-up at 6 months.	MANOVA differences between groups for all dependent variables (pre to post treatment) significant, p <0.04. Post-treatment to follow-up: MANOVA significant for 3 treatment groups, p <0.008.	"[T]he strongest short-term treatment benefits were shown by patients receiving applied relaxation training on measures of pain, distress, interference in daily living, depression and anxiety. By 6-month follow-up, differences between treatment groups were no longer evident."	Study incorporated broad array of ill-defined pain complaints that appear to limit generalizability of results. Inclusion of those with apparently high prevalence rates of signs suggestive of autonomic dysfunction raises questions regarding whether study includes or largely focused on CRPS despite physical

						therapists diagnoses of 3% RSD cases. Baseline differences may have favored EMG biofeedback.
Nouwen 1983 RCT	3.5	N = 20 with chronic LBP, and EMG levels >5µV	EMG biofeedback training (n = 10) vs. wait listed control (n = 10). Both groups received 15 treatment sessions over 3 weeks.	EMG pain scores showed significant main effect between pre-post treatment ($p < 0.0003$), and interaction between groups ($p < 0.0003$). Control vs. EMG had higher pre-treatment EMG levels, $p<0.01$.	"[T]hat reduction of standing paraspinal EMG does not lead to reductions in pain."	Small study.
Stuckey 1986 RCT	3.0	N = 24 with chronic LBP with symptoms ≥6 months	EMG-biofeedback training (n = 8) vs. relaxation training (n = 8) vs. placebo-control (n = 8). All groups received 8 sessions.	Significant decrease at Session 8 in upper trapezius EMG for EMG biofeedback, and relaxation training. Adjusted mean differences for decreasing EMG at Session 8 superior for relaxation training vs. placebo. Mean pain intensity decreased significantly for relaxation training.	"Relaxation training gave better results in reducing EMG and pain, and in increasing relaxation and activity than either EMG biofeedback alone or a placebo condition."	Comparisons among conditions found relaxation significantly superior to placebo and to biofeedback.

Andrasik 1984 RCT	2.5	N = 55 successfully treated for headaches	Regular contact vs. booster treatments for 8 weeks for headache types vascular success, vascular failure, tension success, and tension failure: n = 17/n =11, n = 12/n = 10, n = 11/n = 9, n = 9/n = 7. Final follow-up at 12 months. Regular contact consisted of daily monitoring of headache activity, while booster contact consisted of full session of biofeedback.	Subjects with tension headaches receiving booster treatment had significant peak headache intensity from 3-12 month follow up, p <0.01.	"Headache diary records and interview with patients and significant others revealed no major differences between conditions, indicating regular contact may be an efficient procedure for maintaining treatment gains."	Many details missing. No sham controls. Data suggests comparability.
Vlaeyen 1995 RCT	2.5	N = 71 with chronic LBP	Operant treatment (OP, n = 21) vs. operant-cognitive treatment (OC, n = 18) vs. wait list control (n = 13). Final follow-up at 12 months.	Pre-treatment/6 month follow-up differences for variable outcome efficacy better in OC vs. OR group, p = 0.002. Pre-treatment: 12 month follow-up differences for variable outcome efficacy better in OC vs. OR, p = 0.008.	"During the treatment the three treatment groups improved significantly more than the waiting-list control group on most of the measures."	Randomization arguably not random and not necessarily with blinded assignments done based on whether patient appeared in clinic in first 18 months of study (1 assignment) vs. another time interval (another assignment).

Newton-John 1995 RCT	2.5	N = 44 with history of non-malignant LBP for ≥6 months	EMG biofeedback (EMGBF, n = 16) vs. cognitive behavioral therapies (CBT, n = 16) vs. wait list control (n = 12). Both treatments 1-hour session 2 times a week for 8 weeks. Final follow-up at 6 months.	At 6 month follow up, CBT n = 13, and EMGBF n = 10. ANOVA differences between groups for coping skills questionnaire, pain beliefs questionnaire, and pain diary significant at 6 month follow-up: p <0.05, p <0.01, p <0.001.	"[C]BT and EMGBF are both effective in producing short term improvements in pain intensity, perceived level of disability, adaptive beliefs about pain and the level of depression."	Dropout and compliance rates appear so low that it is not clear that non-responders might not have dropped out artificially, thus amplifying results.
Rokicki 1997 RCT	2.0	N = 45 college undergrads meeting IHS chronic tension-type headache, and having >12 headaches a week	Relaxation training plus EMG biofeedback (n = 30) vs. 3 sessions of an assessment-only control group (n = 14). Both treatments received 2 sessions a week for 3 weeks.	For all statistical tests, α = 0.05. Pre-/post reduction in frontalis, right trapezius, left trapezius using MANOVA significant, p <0.01. For headache variable, group x pre-post interaction significant, p<0.05. Treatment group showed significant improvement in headache activity, and headache free days: p <0.05, p <0.05. Treatment group	"[I]mprovements in tension headache activity achieved with relaxation/biofeedback training are mediated by cognitive changes induced by therapy, at least in young adult tension-type headache sufferers."	Contact time between two groups differed by two-fold, in favor of more contact time in biofeedback and relaxation group.

				had significant higher external locus scores prior to treatment, p <0.05.		

Work Conditioning and Work Hardening Programs

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Corey 1996 RCT	3.5	N = 214 with soft tissue injuries receiving WCB wage loss benefits	Limited functional restoration program (n = 74) vs. usual care (n = 64) for 35 days. Intervention included 6.5 hours a day of exercise, work conditioning, group education, behavioral counseling. Final follow-up 9-27 months.	At follow-up, LFR vs. usual care superior for pain ratings, and sleep ratings: 5.3±2.90/6.5±2.24/p = 0.008, 0.72/0.38/p = 0.002. Return to work rates greater in subjects with LBP, p = 0.002.	"The results of the present study provide support for the efficacy of a limited functional restoration program in reducing subjective pain levels and enhancing return-to-work rates for WCB claimants with chronic pain, particularly low back pain."	Utilization of a usual care group, while simulating real world, might not show efficacy of an intervention as much as futility of usual care. Interestingly, narcotic use did not differ and did not decrease in either group (11.7 pills a week to 13.7 vs. 11.0 to 10.7 for usual care).

Interdisciplinary Pain Rehabilitation Programs

Author/Year Study Type	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Mitchell 1994 RCT	3.5	N = 542 with chronic soft tissue and low back injuries not recovered after 90 days of injury	Functional restoration program (n = 271) vs. control group (n = 271). Both treatments 7 hours a day, 5 days a week, for 8-12 weeks. Intervention included physical exercise, functional stimulation program, behavioral and cognitive therapy, group counseling, and biofeedback.	FRP (n = 71) vs. control (n = 91) had significantly less subjects granted permanent disability, p <0.05.	"Using the difference in total costs as a measure of relative success, back injuries had better results than other injuries in this study."	Only small differences between treated and control groups. Appears aerobic exercise components weak, possibly contributing to suboptimal results.
Strand 2001 RCT	3.5	N = 177 with LBP on long-term sick leave, >8 weeks	Multidisciplinary rehab program (6 hours a day, 5 days a week, n = 81) vs. control (n = 36) for 4 weeks. MRP consisted of physical treatment, education, cognitive/behavioral modification, and workplace intervention. Final follow-up at 12 months.	At 1-year follow-up, 50% returned to work. Statistically significant improvements from baseline to follow-up in returners to work: in intervention group on all tests and in controls on all but 2 performance tests. Improvement measures discriminated between returners and nonreturners to work in intervention group on all physical tests and pain test and in control group on physical and pain tests.	"Return to work was related to physical function and pain. More importance seemed to be attributed to physical performance in the intervention group than in the controls as a basis for returning patients to work."	Stratified results between those working and not working 1 year later showed significant differences between each group.

Peters 1992 RCT	3.0	N = 85 with chronic non-malignant pain lasting ≥ 6 months; most common pain headaches and LBP	Inpatient pain management program (n = 22) vs. outpatient pain management program (n = 18) vs. control group (n = 12) for duration of 4 weeks. In-patient pain program: pain education, EMG feedback, cognitive restructuring/ visualization, exercise, counseling, medication management. Outpatient pain program similar to inpatient program, 2-hour sessions 9 times a week. Final follow-up at 9-18 months.	ANOVA turkey test at pre-treatment showed inpatient program superior to control for pain behavior checklist ($p < 0.05$), and superior to outpatient program for general health questionnaire ($p < 0.05$). Differences between groups for number of treated subjects meeting success criteria at follow up using chi square significant, $p < 0.025$, vs. control.	"[P]ain management programmes contribute substantially to the rehabilitation of chronic pain sufferers."	Patients not well described. Many details sparse.
Härkäpää 1990 RCT	3.0	N = 476 "blue-collar" subjects with LBP ≥10 years, and pain affect their work, physical capacity in Finland	Inpatient treatment (3 weeks at a rehabilitation center, n = 157) vs. outpatient treatment (2 sessions/week for 2 months at work place or center, n = 159) vs. controls (n = 160). Final follow-up at 2.5 years.	Inpatients had significant decrease in LBP vs. outpatients at 1.5 years ($p < 0.02$), and 22 months vs. controls ($p < 0.04$). Differences between groups for long-term gain significant ($p < 0.01$), and between inpatients vs. controls significant ($p < 0.01$). Inpatient vs. outpatient vs. control difference for subjects reporting having done exercise more frequently: $p < 0.01$, $p < 0.01$, $p < 0.05$.	"Pain and disability had decreased significantly in the two treated groups up to the 3-month follow-up. LBP was still a little slighter in the inpatients at the 1.5 year and 22 month follow-ups, but there were no significant differences between the groups in disability caused by LBP."	While stated results statistically positive, actual graphic results and trends over time nearly statistically non-significant and appear clinically poor and may reflect apparently heavy program educational and passive modality components.

Basler 1997 RCT	2.5	N = 76 diagnosed with chronic LBP in Germany	Cognitive behavioral therapy plus prescribed medical treatment (2.5 hours/week, n = 36) vs. control (n = 40) for duration of 12 weeks. Subjects in cognitive group told to keep a pain diary for 4 weeks. Both groups received meds, nerve blocks, TENS, and PT	Interaction group x time for pain intensity, control over pain, avoidance behavior, pleasant activities, catastrophizing, social roles, physical functions, and mental performance: p <0.01, p <0.05, p <0.05, p <0.01, p <0.01, p <0.05, p <0.01, p <0.05.	"Patients who only received medical treatment showed little improvement."	Dropout rates concerning and baseline differences may have consequently occurred.

REHABILITATION FOR DELAYED RECOVERY

Author/Year Study Type Potential Conflict of Interest (COI)	Score (0-11)	Sample Size	Comparison Group	Results	Conclusion	Comments
Back School/Education						
Lønn 1999	3.5	N = 81 workers with LBP in past year	Secondary prophylaxis plus active back school (ABS, n = 43) vs. no treatment (n = 38). Treatments consisted of 20 sessions (20 minute theoretical part plus 40 minute exercise part) in 13 weeks. Follow-up at 12 months.	ABS vs. control for number of LBP sick days over 1 year: 10.4±9.3 (1.8-19)/ 37.8±28 (19-56.6). First 12 months, ABS less new LBP episodes/ duration of sick leave. At 12 months, significant increase in LB function score. From baseline to 5 and 12 months, BEF tests improved in ABS group. At 12 months, ABS improved quality of life, p = 0.03.	"Active Back School reduced the recurrence and severity of new low back pain episodes according to results of follow-up examinations performed 5 and 12 months after enrollment."	No blinding. Total compliance defined as attendance at 20 sessions, 75% compliance. Allowed use of other treatments and participation in physical activities. Data suggest back school successful.

Berwick 1989	3.5	N = 222 with LBP ≥6 months, and no prior back surgery	Usual care (UC) (n = 74) vs. 4 hour low-back school (n = 72) vs. compliance package (low back school plus 1 year compliance program to promote LBP self-management, n = 76). Final follow-up at 18 months.	At 3 months, UC had greater psychosocial scale score, p = 0.02. At 12 months, UC subjects with baseline VAS of ≥2 pain free, p = 0.048.	"[A] short version of Back School, with or without follow-up reinforcement contacts, is unlikely to affect the course of pain and disability for a relatively unselected group of victims of LBP in an ambulatory environment."	Several methods not specified. Usual care likely did not include typical modern care.
Donchin 1990	3.5	N = 142 with ≥3 episodes of LBP a year	Calisthenics (3 months with biweekly 45 minute sessions of flexion exercises, n = 46) vs. back school program (n = 46) vs. control (n = 50). Final follow-up at 6 months.	At 3 and 6 months, calisthenics group had improved trunk forward flexion plus abdominal muscle, p <0.0001. Differences between groups, p <0.003 adjusted for sex. At 6 months, calisthenics vs. other groups had significant improvement in trunk forward flexion, p = 0.019.	"The current study clearly demonstrates the effectiveness of the calisthenics group in reducing the number of recurrent LBP episodes."	Wait-listed controls biases against that group. Baseline measurements of trunk forward flexion, Schober's test, SLR Rt, and abdominal muscle strength score collected for only men.
Julkunen 1988	3.5	N = 204 females with chronic LBP ≥1 year in Finland	Back school treatment (n = 95) vs. control (n = 93). Treatment group consisted of 1 hour meetings 6 times for 3 weeks conducted by physiotherapist. Control received back school treatment in written form. Final follow-up at 12 months.	Difference on HYS scale for good responders (+) for control vs. poor responders (-) to controls, p = 0.05. Difference in Rorschach R variable back school + vs. control -, back school - vs. control +, and control + vs. control -: p = 0.02, p = 0.01, p = 0.02.	"[T]hose patients who reacted favorably to the back school intervention could be described as emotionally well adjusted and controlled showing relatively good cognitive capacity with undisturbed reality testing."	Rorschach scorer blinded. Data suggest efficacy.
Lankhorst 1983	3.5	N = 48 with idiopathic LBP ≥6 months	Back school sessions (4 over 2 weeks, n = 21) vs. detuned pulsating shortwave applications (n = 22). Final follow-up at 12 months.	Both groups had increased active SLR, decrease in spinal mobility, and increase in functional capacity. Back school subjects had decrease in functional capacity and increase in pain immediately after treatment.	"Given the proven efficacy of the Back to School in (sub)acute Low Back Pain, it should be administered when it is most beneficial, i.e. in the early phase of Low back Pain."	Quasi-randomized; subjects allocated in groups of 6 consecutive patients.
Bergquist-Ullman 1977	3.5	N = 217 workers with acute or subacute LBP	Back school (45 minute sessions 4 times a week for 2 weeks, n = 70) vs. combined physiotherapy (n = 72) vs. placebo (n = 75).	Back school vs. combined physiotherapy vs. placebo sick days during initial pain in treatment groups at ≤21, >21 days, and total: 37/30/25, 18/31/41, 55/61/66.	"[B]ack School and combined physiotherapy are superior to "placebo" treatment in acute low back pain. The Back	100% attendance at all back school sessions; only 59 control group followed treatment; 4 drop outs in

		<3 months in Sweden		Difference between groups significant, p <0.01.	School also reduces the absence from work."	combined physiotherapy group.
Versloot 1992	3.5	N = 500 with LBP working as drivers for a Dutch bus company	Individualized back school program (3 sessions with 6 month intervals between sessions, n = 200) vs. control (n = 300). Both treatments administered for 2 years. Study lasted 6 years.	Between 2 years during treatment-2 years after treatment, decrease in length of short absenteeism for control group, p <0.046. At 6 years, decrease in length of absenteeism for back school, p <0.024.	"Although the internal validity of this study may be criticized, results indicate that a tailor-made back school program given by expert instructor was capable of reducing absenteeism."	Sample population randomized into groups (North and South). First back school session mandatory, but sessions 2 and 3 voluntary. Subjects not described.
Roberts 2002	3.5	N = 64 with recent acute LBP	Back Home leaflet in addition to regular advice and management (n = 35) vs. regular advice and management (n = 28). Final follow-up at 12 months.	At Week 2, easiest position for putting on socks/tights attitude question significantly increased, p = 0.036. Differences at 2nd day/2 weeks/3 months/6 months significant for behavioral observation.	"The Back Home trial has shown that a simple leaflet may be a useful adjunct to management strategies that is particularly well suited to primary care."	Researcher blinded. Data suggest leaflet helpful, but many study weaknesses.
Moffett 1986	3.0	N = 92 with chronic LBP ≥6 months	Back school program (n = 40) vs. exercise-only program (n = 38). Back school with 3 sessions of anatomy/biomechanics education, ergonomic lifting exercises, and ergonomic counselling. Exercise only with ergonomic lifting exercises. Both programs 3 times a week. Follow-up at 6 and 16 weeks.	Baseline vs. 6 week differences between groups for activity: p <0.001, p <0.001. Baseline vs. 16 weeks for quiz: p <0.05, p <0.05; 6 weeks vs. 16 weeks for pain, and functional disability: p <0.05/NS, p <0.05/p <0.01.	"[A]ll chronic back pain patients would benefit from a program of back care education, such as is offered by the back school. It can be considered an important adjunct to other forms of treatment, both conservative and surgical."	Dropout rate high at 16 weeks (39/92), precluding strong conclusions.

Penttinen 2002	3.0	N = 93 with non-specific LBP ≥1 month	Back school with social support (2 sessions/week for 10 weeks, n = 47) vs. control (2 sessions a week for 5 weeks, n = 46). Follow-up at 6 and 12 months.	Six vs. 12 month differences between groups for Oswestry index disability score, and life quality score: p = 0.25/p = 0.02, p = 0.04/p = 0.19. For males, difference in trunk extension force (Nm) at 6 months significant between groups: p = 0.04. For females, difference in trunk extension force (Nm), and VO_{2max} (ml kg^{-1} min^{-1}) at 6 months significant between groups: p = 0.05, p = 0.05.	"[S]ocial interaction between patients suffering from non-specific back pain reduces subjective disability."	Dropout rate and baseline differences concerning. Compliance unclear. Intervention period may have been too short to see changes in objective measurements. Post-hoc data suggest better results among males.
Maul 2005	2.5	N = 148 with LBP ≥2 months preceding year before recruitment	Back school (3 1-hour sessions, n = 86) vs. back school plus supervised physical training (training therapy twice a week plus back school once a week for 3 months, n = 97). Follow-up at post-treatment, 6 months, 1 year, and 10 years.	Differences between groups measured at pre- vs. post-treatment vs. 6 months for muscular endurance index, strength isokinetic index, lifting index, ROM: p = 0.0001, p = 0.006, p = 0.001, p = 0.01. Differences between groups measured pre- vs. post-treatment vs. 6 months vs. 1 year for pain drawing, current pain (NRS), pain (Mc Gill), disability (Waddell), and disability (Roland Morris): p = 0.001, p = 0.0001, p = 0.0001, p = 0.002, p = 0.005.	"[S]upervised physical training applying strengthening exercises effectively improved objective functional outcome parameters and subjective self rates disability and pain scores during short-term follow-up."	Large dropout rates (from 358 to 148) limit conclusions. For all follow-ups, participation ranged from 66-96%. Data suggest long-term benefits if weaknesses not fatal.
Sirles 1991	2.5	N = 74 city employees with back injuries	Back school education with exercise (exercise 6 times a week, n = 29) vs. counseling intervention (n = 45). Treatment once a week for 6 weeks.	Baseline 6 week differences in anxiety (Spielberg) score, and depression inventory (Beck) significantly less in back school group: p = 0.03, p <0.01. At Week 6, significant increase in flexibility between groups, p <0.01.	"No significant differences were found, on any of the measures, between employees who did and who did not receive the counseling intervention."	Intervention occurred during work hours. Only subjects who completed both pre-and post-tests included in analyses.
Lindequist 1984	2.5	N = 56 with acute LBP	Back school program (n = 24) vs. control (n = 32). Final follow-up at 1 year.	In year of follow-up, 16% in treatment group had LBP recurrence vs. 31% controls; not statistically significant.	"[T]he initial treatment could be limited to advice about back care, preferably a few days bed-rest, with concrete advice about the back and prescriptions for analgesics when needed."	Subjects took advantage of extra physiotherapist visits an average of 2.4 times over 6-week period; 3 patients in each group required more than 100 days of sick-leave.
Postacchini	See Manipulation and Mobilization under Physical Methods above.					

1988						
Schenk 1996	2.0	N = 205 healthy subjects with previous LBP	Back school education (n = 74) vs. video group (n = 64) vs. control (n = 67).	"No significant differences were found between the video and control groups on the measures with additional univariate testing."	"[T]he back school is an effective tool for influencing lifting posture and conveying information regarding spinal mechanics and lifting technique. In addition, the back school videos may not be an effective means of preventing low back injury."	Methods discuss potential randomization failure. Appropriateness of lordotic lifting posture for manual patient transfers dubious as unlikely to reduce intradiscal pressures with long horizontal distances required.
Overmeer 2011 RCT The Department of Occupational and Environmental Medicine at Orebro University Hospital funded this research. No mention of COI.	N/A	N = 42 physical therapists	Course group went to an 8 day university course identifying and addressing psychosocial prognostic factors (n=22) vs. control group was put on a waiting list (n=20). The physical therapists then saw 266 patients to compare treatment efficacy. Last follow-up was at 6 months.	No difference was seen in pain in patients (F = 0.85; df = 1,225; P = 0.9) or disability (F = 1.1; df = 1,222; P = 0.03). No differences were found when patients in the risk group saw a physical therapist who took the course than the one who did not take the course (F = 2.38; df = 1,221; P = 0.1).	"An 8-day university course for physical therapists did not improve outcomes in a group of patients as a whole or in patients with a risk of developing long-term disability. However, patients who had a risk of developing long-term disability and had higher levels of catastrophizing or depression may have shown greater reductions in disability if the attitudes and beliefs of their physical therapists changed during the course."	RCT of educational course for PTs. Exclude.
Stapelfeldt 2011	0	N = 351 employees ages 16 to 60 years, requiring	Brief intervention (clinical exam and advice) (N = 175) vs	Work and health-related models were the biggest indicator of whether an intervention worked or not depending upon individual.	"[P]articipants with low job satisfaction, no influence on work, no interest in returning to the same job and at risk of	Secondary analyses of Jensen C, Jensen OK, Christiansen DH, Nielsen CV: One-year follow-up.

RCT No mention of industry sponsorship or conflict of interest (COI).		sick leave for 3-16 weeks due to back problems.	Multidisciplinary (clinical exam, advice, multidisciplinary team, and case worker) (N = 176).		losing their job seemed to return earlier to work when they received the multidisciplinary intervention, whereas participants without these characteristics returned to work earlier when they received the brief intervention."	

Chronic Regional Pain Syndrome

Aerobic Exercise

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Topcuoglu 2015 (3.5)	CRPS	RCT	No COI or sponsorship.	N = 40 hemiplegic, admitted for subacute inpatient stroke rehabilitation, diagnosed with CRPS I	18 female, 22 male. Mean age exercise group 65.95±8.7 years, control group 67.5±11.2 years	Conventional standardized CPRS type I physiotherapy – TENS analgesic current, cold-packs, retrograde massage, contrast baths (N = 20) vs Addition of aerobic exercise program with arm crank ergometry (N = 20)	4 weeks	Exercise group presented less hyperalgesia (P=0.005), metacarpophalangeal joint tenderness (P=0.002), tenderness upon wrist extension (P=0.005), and hand sweating (P=0.0013). General linear repeated measures: Shoulder region – VPS score improvement in exercise group significant (F=5.293, P=0.027), not significant on night pain (F=0.082, P=0.776) or on movement pain (F=3.410, P=0.073), Hand region – VPS	"Aerobic exercises should be prescribed in addition to the conventional treatment of CRPS in order to increase the functional independence of hemiplegic patients with CRPS, to improve their participation in the activities of daily life, to reduce their depressive symptoms, and to improve their general well-being. Aerobic exercises should be prescribed for hemiplegic	Stroke patients with CRPS only. Exercise intervention is not standardized or reproducible. Data suggest aerobic exercise of additive benefit.

								score improvement in exercise group significant (F=8.284, P=0.007) and in movement pain (F=6.796, P=0.013), not significant on night pain (P=2.003, P=0.165)	patients with CRPS."	

DMSO

Author Year (Score):	Category	Study type:	Conflict of Interest	Sample size:	Age/Sex	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Zuurmond 1995 (3.5)	DMSO	RCT	No mention of sponsorship or COI.	N=31 individuals diagnosed with Acute Reflex Sympathetic Dystrophy (RSD).	14 males, 17 females: Mean age group 1: 47 (40-61), group 2 : 48 (41-68)	Group 1 (N=16) patients received fatty cream with 50% dimethyl sulfoxide (DMSO). vs Group 2 (N=14) patients received fatty cream without DMSO	Follow up at baseline and 2 months (check in every two weeks within follow up)	RSD median score difference, baseline to 2 month difference, group 1 vs 2 (Median (Min-Max)): 4 (0-5) vs 3 (0-5) ($p<0.01$). No difference in Visual analogue scale. Side effects include some skin scaling and garlicy taste and odor after using DMSO cream.	"We conclude that treatment of acute RSD with DMSO 50% added to white soft paraffin-cetomacrogol-cream and physiotherapy is recommendable. "	Methodological details sparse. RSD score difference between groups, but there were no differences in pain outcomes.

Tumor Necrosis Factor-Alpha Blockers

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Dirckx 2013 (3.5)	CRPS	RCT	No mention of sponsorship or COI	N = 13 with CRPS	Mean age 47.8. 13 female.	Treatment group infliximab (5mg/kg) in saline solution (0.9%) administered at weeks 0, 2, and 6. N = 6 Placebo saline solution (0.9%). N = 7 at weeks 0, 2, 6.	6 weeks.	No significant change in ISS score between 2 groups. No significant difference in cytokine levels. Treatment group showed greater reduction of TNf-alpha. Decrease in health status in the intervention group.	"This study was terminated before the required number of participants had been reached for sufficient statistical power. Nevertheless, a trend was found toward an effect of infliximab on the initially high TNF-a concentration."	Small sample size (n=13). Participant flow and exclusion poorly described. Co-interventions poorly described. Trial terminated prematurely.

Regional Sympathetic Blocks

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Rocha 2014 (3.5)	Thoracic sympathetic blocks	RCT	No COI. Supported by The Pain Center, Neurology Department, University of São Paulo, Brazil.	N = 36 diagnosed via The International Association for the Study of Pain 1994 for CRPS type I, pain for at least 6 months, pain relief failure after conventional treatment	19 female, 17 male. Mean age 44.7 years	Thoracic sympathetic blocks, 10 mL of anesthetic + corticosteroid solution (5 mL of 0.75% ropivacaine, 5 mL of 2% triamcinolone) injected into T2 sympathetic thoracic ganglion, paralateral to T2 vertebrae on affected side (N = 17) vs control, sham injection (N = 19)	12 months	Mean Brief Pain Inventory pain intensity at month 1: TSB (3.59 ± 3.2), Control (4.84 ± 2.7) (P = 0.249). At 12 months TSB (3.47 ± 3.5), control (5.86 ± 2.9) (P = 0.046). Mean BPI difference from baseline at 1 month – TSB (5.59 ± 2.9 to 3.53 ± 3.7, P = 0.035), Control (6.16 ± 3.0 to 5.84 ± 2.9). Mean McGill Pain Questionnaire scores at 1 month – TSB (36.56 ± 16.2), Control (42.33 ± 8.5) (P = 0.024). 12 month – TSB (27.20 ± 22.2), Control (45.43 ± 23.6) (P = 0.042).	"In conclusion, our data showed that a single TSB is a safe procedure and has both short- (1-month) and long- (12-month) term positive impact on upper limb CRPS type I as an add-on treatment to a standardized rehabilitation and pharmacological treatment program. While the impact of the procedure on quality of life is slightly significant, pain reduction, decrease in evoked pain, and amelioration of depressive symptoms, were significantly superior to the control treatment."	Methodological details sparse. Poor description of intervention and comparison treatments and co-interventions. Difficult to replicate based on description.

Desensitization Techniques for CRPS

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Length of Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Fialka, 1996 (score=1.5)	CRPS	RCT	No mention of Sponsorship or COI.	N = 18 patients with reflex sympathetic dystrophy of the upper limb	Mean age: Control Group: 63.4±3.7 Training Group: 64.2±6.6 Sex(M:F) 6:12	Autogenic Training group (N =9) received home therapy and autogenic training once a week for 10 weeks. vs Control group (N =9) received home therapy.	*10 weeks*	Both groups experienced pain relief over the trail period. Skin temperature significantly decreased in Training Group, in comparison, the Control group demonstrated a slight numerical increase. (Training group reduction: 2.3°C vs Control group change +0.8°C (p<0.006))	"It is concluded that autogenic training may be helpful in certain aspects of reflex sympathetic dystrophy but its potential value requires further study."	Methodological details are sparse. No differences in pain score, range of flexion, range of extension and volume difference between hands. Skin temperature was different between treatment and controls co-interventions poorly described.

Ketamine

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Schilder 2013 (2.5)	CRPS	RCT secondary analysis	No COI. Supported by a grant from the Dutch Ministry of Economic Affairs.	N = 19 patients with CRPS I in the arm, participating in a ketamine-placebo trial	15 female, 4 male. Mean age placebo group 47.0 years, ketamine group 42.3 years	S(1)-ketamine (N = 15) vs placebo/saline (N = 14). Both administered through intravenous infusion for 4.2 days	12 weeks	Linear mixed model analysis – a pain increase of 1 on the numerical rating scale (NRS) pain was associated with reduced velocity of 1.14 cm/s (95% CI = -2.00 – -0.27, P = .011), with reduced frequency of 0.07 Hz (95% CI = -0.13 – -0.01, P = .023), and with a decrease in amplitude of 0.19 cm (95% CI = -0.35 – -0.03, P = .023). Higher NRS pain scores significantly associated with various arrests: 1 point increase led to 4.26 extra arrests during 15 seconds of finger tapping (95% CI = 2.19 – 6.34, P < .001).	"To summarize, our results show that at each time point pain scores were directly related to motor function in CRPS, irrespective of whether patients received ketamine or placebo. Pain relief should be regarded as an important treatment goal in the management of motor disturbances in CRPS patients."	Methodological details spares. Secondary analysis of ketamine study. No meaningful difference between treatment groups at 12 weeks.

Magnesium Sulfate

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Collins 2009 (2.5)	CRPS	RCT	No mention of sponsorship or COI	N = 10 with CRPS 1 patients	Mean age 44. 8 women 2 men.	Received 70mg/kg magnesium sulphate infusions 4 hours for 5 days. N = 8 Vs Control received NaCl 0.9% solutions N = 2.	1 week	Reduced pain at follow up vs baseline. (T1: p = 0.01,T3: p = 0.04, T6: p = 0.02 T12: p =0.02) McGill sensory improvement T1: p = 0.03 pain rating index p = 0.01. Impairment level (p = 0.030). Quality of life (EuroQol p = 0.04, SF-36 physical p = 0.01)	"Intravenous magnesium significantly improved pain, impairment and quality of life and was well tolerated."	Methodological details sparse.

Injections

Safarpour 2011 (score=2.0)	CRPS	RCT	Jabbari serves on the advisory board for Allergen Inc. the Supported by Allergen Inc.	N = 8 with CRPS (according to the International Association for the study of PAIN [ISAP]) with allodynia	5 female, 3 male. Mean age 47.12 years	Botulinum (BoNT) toxin (N = 4) vs Saline (N = 4)	3 weeks, 2 months	Mean average pain intensity at baseline: BoNT 8.25, Saline 7, (*P* ⍰⍰0.05). At week 3 and 2 months – mean pain days: Placebo 24.8, BoNT 28.0, (*P* = 0.391), mean maximum pain intensity – BoNT 3 week 8.5 (P = 0.215), 2 month 8.3 (P = 0.182), Saline 8.5 (P = 0.215), 8.3 (P = 0.638). Average pain – 3 week BoNT 7.5 (*P* = 0.215), 2 moths 7.3 (*P* = 0.182), Saline 7 (*P* ⍰⍰0.5), 6 (*P* = 0.252). Study stopped prematurely due to lack of pain relief and no improvements	Intradermal and subcutaneous administration of BoNT-A into the allodynic skin of the patients with complex regional pain syndrome (CRPS) failed to improve pain and was poorly tolerated."	Study stopped early due to adverse events, participants reported "Injections intolerable" and "patients indicated that even if the injections work, they will not consider this mode for treatment due to extreme level of discomfort." Methodological details sparse.

Lidocaine Infusions

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Wallace 2000 (2.5)	Lidocaine	RCT	Supported by the international Anesthesia Research Society. No mention of COI.	N=16 patients with Chronic Regional Pain Syndrome (CRPS) stage I and stage II.	7 females, 9 males; mean age of 44±15.	Group 1 Received intravenous lidocaine achieving a 1ug/ml to 3 ug/ml concentration. vs Group 2 received placebo diphenhydramine.	Patients were followed up at baseline, 1 and 2 weeks.	Plasma level 3 ug/ml, lidocaine produced a higher "Hot Pain" threshold from 44.7°C to 47.9°C ($p<0.05$). Lidocaine had significant decrease in response to stroking, cold allodynia, cool stimulus, and spontaneous pain. Side effects: lidocaine produced significantly more light headedness in patients, also significantly raised Systolic Blood pressure 134.9±20.2 mmHg to 150.6±21 mmHg in 3 ug/ml group.	"Lidocaine is an example of a drug that may be the choice for pain that has a strong cool-evoked component. Until further studies are completed with different classes of agents, we can make no further conclusions on how to select the drugs."	Small sample size (n=16). Methodological details sparse. Short term study of 2 weeks.

Spinal Cord Stimulators

Author Year (Score):	*Category:*	*Study type:*	*Conflict of Interest:*	*Sample size/Population:*	*Age/Sex:*	*Comparison:*	*Follow-up:*	*Results:*	*Conclusion:*	*Comments:*
Kemler, 2001 (3.0)	Spinal Cord Stimulation	RCT	No mention of COI or sponsorship.	N=54 patients with chronic complex regional pain syndrome	Mean age: 38.4 years. 17 males, 37 females.	SCS+PT: Received spinal cord stimulation and physical therapy (n=36) vs PT: received only physical therapy (n=18)	3, 6, 12 months	No significant difference was observed in SCS patients and control from T1 to T5.	"Although SCS has previously been shown to cause a significant pain reduction in complex regional pain syndrome type I, the treatment has no long-term effect on detection and pain thresholds for pressure, warmth, or cold. The treatment seems to have only minimal influence on mechanical hyperalgesia."	Spinal cord stimulator only implanted in responsive patients, not truly randomized study for all participants.
Meier 2015 (3.5)	Chronic, CRPS	RCT	This PhD study was funded by Aarhus University, Aarhus, Denmark, St Jude Medical, St. Paul, Minnesota and the Danish Medical Research	N = 14, 5 patients with CRPS, and 9 with chronic pain due to peripheral nerve injury.	Mean age 53, 9 female, 5 male.	One group (N = 7) following quantitative sensory testing (QST) had spinal cord stimulation (SCS) for a 10-12 hour interval. The other group (N = 7) received no SCS for 10-12 hours after QST. After the	Follow-up consisted of QST 3 times: at baseline, and after each (2) 12 hour treatment session.	No statistically significant results were seen in any 3 QST from both groups. There were no significant changes in mechanical or thermal thresholds, nor intensity of pain, or reduction of areas with painful symptoms.	"[D]ata seem to suggest that active SCS treatment does not change sensory perception. In addition, there was no significant change in pain intensity, suggesting a chronic effect of SCS in long-term	Small sample size (n=15). Short duration. Methodological details poorly described.

			Council, Copenhagen, Denmark. Authors K.M. and J.C.S. have teaching funding from St Jude Medical and are paid consultants for Biolab Technology.			12th hour, groups switched treatments of SCS for another 10-12 hours.			implanted patients rather than acute changes."	
Eckmann 2011 (2.5)	CRPS	RCT	No mention of sponsorship or COI	N = 10 with unilateral CRPS I (International Association for the Study of Pain modified diagnostic criteria).	N=10 aged ≥18	Each patient was Randomized to receive 4 IVRB treatments 1 week apart. Each patient received a standard 50mL lidocaine 0.5%. The dose of ketorolac 0, 30, 60 and 120 mg was a randomized order.	4 weeks	1 outcome showed significant improvement. 2 day pain reduction in the ketorolac groups (median NRS 6 to 4 (p= 0.002)). Overall pain NRS week 1 6.2 ± 0.53, 6.5 ± 0.89, 6.0 ± 0.88, 5.9 ± 1.07 and 5.8 ± 0.9 at baseline 0, 20, 60, 120mg. (p = 0.80 pain with movement. 7.15 ± 0.69, 5.7 ± 1.07, 6.1 ± 0.86, 5.0 ± 0.97, and 5.6 ± 0.86, (p =0.059. Edema 2% reduction (p = 0.6).	"IVRB with ketorolac and lidocaine produced only short-term pain reduction in patients with CRPS involving the lower extremity after 4 serial injections"	Methodological details sparse.

Fibromyalgia

Cytokine Testing

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Imamura 2014 [3.0]	Cytokine testing	Diagnostic								Data suggest both FM patients and Knee OA patients have similar levels of cytokines.
Geiss 2012 [2.5]	Cytokine testing	Diagnostic								Small sample. Data suggest that on altered glucocorticoid function, not reduced cortisol levels may be the reason for the core FM symptoms.
Gur A, 2001 [2.5]	Cytokine testing	Diagnostic								Data suggests IL-8 may be key in FM pain.

Antibodies

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Dejaco 2006 (3.0)										Population included mixed rheumatological patients. Data suggests anti-CCP2 is very specific and a

										better diagnostic test than anti-MCV for RA.
Ribeiro 2004 (2.5)										Data suggests a correlation between FM and thyroid autoimmunity.

Platelets

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Elmas 2016 (2.5)										Data suggest that TEMP and PLT were higher in fibromyalgia group versus controls.

Non-Specific Inflammatory Markers for Screening for Inflammatory Disorders

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Xiao, 2013 (3.5)	Erythrocyte Sedimentation Rate, CRP	Diagnostic	Supported by RGK Foundation, NO COI.	N = a total 166 patients, consisting of 105 patients with Fibromyalgia syndrome (FMS) and 61 healthy patients (HNC).	Mean age: FMS group 49.7±1.1 HNC group 42.7±1. 4Sex(M:F) 16:150	Fibromyalgia	Erythrocyte Sedimentation Rate (ESR) in patients diagnosed with FMS (N=105) in comparison to healthy patients (N=65).	ESR (mm/h) in FMS group vs Healthy patient group (24.8±2 vs 20.2±1.8 (p = 0.08))	"This study has documented, in a subset of FMS patients, elevated serum hsCRP levels which statistically associate with ESR, IL-8, and IL-6. These data suggest that inflammation may contribute to the disease pathogenesis in a subset of obese FMS patients."	Data suggest serum CRP concentrations are higher in fibromyalgia and are highly correlated to BMI, ERR, IL-8 and IL-6 levels suggesting that these inflammatory markers may contribute to some of the obese fibromyalgia patients.

Autonomic Nervous System Testing

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Ozkan, 2015 (3.5)										Data suggest a relationship between FMS and SSR.
Naschitz, 2002 (3.5)										Mixed population of chronic fatigue syndromes, fibromyalgia,

										neutrally mediated syncope, generalized anxiety disorder, nonchronic fatigue syndrome, Mediterranean fever, arterial hypertension and health subjects. Data suggest there is dysautonomia in chronic fatigue syndrome which does not appear to occur in other groups.
Cohen 2000 (2.5)										Data suggest autonomic dysfunction in fibromyalgia.
Doğru 2009 (2.0)										Data suggest increased sympathetic and decreased parasympathetic activity occur in fibromyalgia patients.
Ozgocmen (2.0)										Data suggest no difference between groups.

Functional MRIs

Author Year Score	Category	Study type	Conflict of Interest	Number	Age/Sex	Area	Diagnoses:	CT used no	MRI used	T1 weighted images	T2 weighted images	X-ray no	Myelography	More than one rater	Surgery Performed	Clinical Outcomes	Long-term Follow-up (mean when noted)	Results	Conclusion	Comments
Harris 2009 (3.5)	*fMRI*	*Diagnostic*																		*Data Suggest Fibromyalgia patient shave higher insular glutamate within the posterior insula which may be involved in Fibromyalgia pathophysiology.*

SPECT/PET

Author Year (Score):	Study type:	Sample size:	Age/Sex:	Area of head:	Diagnoses:	SPECT or SPET:	MRI or CT:	More than one rater:	Surgery Performed:	Clinical outcomes assessed:	Long term follow-up: (mean when noted)	Results:	Conclusion	Comments:
Gur 2002 (2.5)	*Diagnostic*													*Cytokines and CB7 can be evaluated using SPECT.*

Surface EMG

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Elert 2000 (3.0)	Surface EMG	Diagnostic	No mention of sponsorship or COI.							Data suggest chronic patients have elevated muscle tension and depressed output during dynamic activity compared to healthy controls.
Westgaard 2013 (2.5)	Surface EMG	Diagnostic	Study sponsored by the Swedish Research Council. No COI.							Data Suggest fibromyalgia patients show increased trapezius activity in stress situations.
Nilsen 2006 (2.5)	Surface EMG	Diagnostic	Sponsored by the Norwegian Research Council.							Data suggest both Fibromyalgia Syndrome and chronic shoulder/neck pain groups required longer recovery time after pain stimulation.

Functional Capacity Evaluations (FCEs)

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Vallejo, 2010 (score=3.0)										Data suggest ICAF is a comprehensive FM severity tool.

F-Wave

Author Year (Score)	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Cakir, 2011 (score=2.5)										Data suggest FM patients have dysfunction in their autonomic nervous system.

Aerobic Exercise

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Giannoti 2014 (3.5)	Aerobic Exercise	RCT								This is a randomized case control. Data suggest EG showed a trend towards improved FIQ, VAS, HAQ and FSS with significant improvement in the 6 minute walking test.
Genc 2015 (3.5)	Aerobic Exercise	RCT								Data suggest exercise can influence Fibromyalgia symptoms and effect HPA but study inconclusive for superiority of aerobic exercise.

Sañudo 2015 (3.5)	Aerobic Exercise	RCT								Usual care bias. Data suggest increasing cardiovagal modulation via aerobics can improve HRV and also improve anxiety and depression.
Garcia-Martinez AM, 2011 (3.5)	Exercise	RCT								Usual care bias. Data suggest PE groups had significant improvement in self-esteem and self-concept, physical flexibility and function and pain.
Richards SCM, 2002 (3.5)	Exercise	RCT								Poor compliance. Data suggests aerobic exercise lead to better participant reported improved outcomes.
Gowens SE, 2001 (3.5)	Exercise	RCT								Data supports exercise as an effective tool for treatment of fibromyalgia patients to improve mood and function.
Martin L, 1996	Exercise	RCT								Data suggest exercise is beneficial in the

(3.5)										short term management of fibromyalgia.
McBeth J, 2012 (3.5)	Exercise	RCT								Questionnaire compliance was only about 33%.
Giannotti E, 2014 (3.0)	Exercise	RCT								Small sample. High dropout rate in control group.
Dobkin PL, 2005 (3.0)	Exercise	RCT								Poor compliance making conclusions difficult.
Koulil SV, 2011 (3.0)	Exercise	RCT								Waitlist control bias. Data suggest physical fitness improved following CBT.
Koulil SV, 2010 (3.0)	Exercise	RCT								Waitlist control bias. Data suggests CBT and exercise improved pain and fatigue both short and long term.

Gowans SE, 2002 (2.5)	Exercise	RCT								Data suggests BDI cognitive and STAI are best test to measure exercise induced changes which effect mood.
Burckhardt CS, 1993 (2.5)	Exercise	RCT								Data suggests comparable efficacy between the education and education plus physical training group.
Van Santen 2002 (2.0)	Aerobic Exercise	RCT								Small sample with high dropout rate. Duration of complaints in years is dissimilar between groups as well as mean age. Where Low Intensity groups was older. Conclusions difficult to ascertain.
Newcomb LW, 2011 (2.0)	Exercise	RCT								Baseline characteristics incomplete. Data suggests women with FM favored lower intensity prescribed exercise.
Padawer WJ, 1992	Exercise	RCT								Data suggests no analgesic effect for

(2.0)										exercise. Sparse methods.
Mayer BB, 2000 (2.0)	Exercise	RCT								Pilot study with same numbers in each groups preventing conclusion statement regarding efficacy. High dropout rate.
Bjersing JL, 2012 (2.0)	Exercise	RCT								Data suggests IGF-1 concentrations did not change between groups but there was a positive correlation between IGF-1 and the pain threshold.
Bement MKH, 2014 (1.5)	Exercise	RCT								Small sample. Data suggests pain response in associated with change in corticomotor excitability.
Sanudo B, 2012 (1.5)	Exercise	Longitudinal study								Data suggests long term exercise training can sustain the immediate gains for 30 months measured by FIQ.

Evidence for Strengthening, Stabilization, and Resistance Exercises

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Bircan C 2008 (3.5)										Data suggest comparable efficacy.
Torres JR, 2015 (3.5)	Manipulation and mobilization	RCT								Usual care bias. Data suggests some improvement in pain and fatigue in active neurodynamic mobilization group.
Garcia-Martinez AM, 2011 (3.5)										Usual care bias. Data suggest PE groups had significant improvement in self-esteem and self-concept, physical flexibility and function and pain.
Martin L, 1996 (3.5)										Data suggest exercise is beneficial in the short term management of fibromyalgia.

Giannotti E, 2014 (3.0)										Small sample. High dropout rate in control group.
Hammond A, 2006 (3.0)										High dropout rate. Data suggests CBT plus exercise group reported more FM symptom improvement (47% vs 13%) at 8 months.
Kaleth AS, 2013 (3.0)										Data suggests MVPA group showed improved well-being and physical function.
Paolucci T, 2015 (3.0)										Data suggest a trend for APA to improve efficacy as measured in FIQ.
Koulil SV, 2011 (3.0)										Waitlist control bias. Data suggest physical fitness improved following CBT.
Koulil SV, 2010										Waitlist control bias. Data suggests CBT and exercise

(3.0)										improved pain and fatigue both short and long term.
Fontaine KR, 2010 (2.5)										Randomization failure – significant difference in number of years since diagnosis of FM (5.9±5.1 vs. 9.6±6.8)
Román P 2015 (2.5)										Data suggests 18 weeks of 60 min/day X 3 day/week combined in water and hand based exercises improved FIQ and VAS
Häkkinen A 2001 (2.5)										Data suggests 21 weeks of strength training can improve the neuromuscular system of both FM and healthy premenopausal women.
Panton L (2.5)										Subjects given incentive to participate. Data suggest similar efficacy improving

										strength and functionality.
Valkeinen H 2005 (2.5)										Sparse methods with missing baseline data. Data suggests strength training increases strength and CSA in elderly FM patients.
Häkkinen K 2001 (2.5)										Small sample. Data suggest progressive strength training yields significant benefits to both FM premenopausal women and healthy premenopausal women
Kingsley 2009 (2.5)										Non-randomized before and after trial data suggest there appears to be altered modulation of the autonomic system in response to acute RE in fibromyalgia patients.

Gavi 2013 (2.5)										Baseline dissimilarities between group for age, anxiety, and grip strength. Data suggest strengthening better than flexibility for reduction of pain and improved strength in fibromyalgia.
Kingsley 2010 (2.0)										Small sample, non-randomized. Data Suggest RET may reduce the Fibromyalgia severity but also not affect the autonomic modulation of heart rate.
Bement M 2011 (1.5)										Small sample, missing baseline data. Pain perception not measured during exercise.

Evidence for Stretching Exercises (Non-Yoga)

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Garcia-Martinez AM, 2011 (3.5)										Usual care bias. Data suggest PE groups had significant improvement in self-esteem and self-concept, physical flexibility and function and pain.
Richards SCM, 2002 (3.5)										Poor compliance. Data suggests aerobic exercise lead to better participant reported improved outcomes.
Martin L, 1996 (3.5)										Data suggest exercise is beneficial in the short term management of fibromyalgia.
Giannotti E, 2014 (3.0)										Small sample. High dropout rate in control group.
Valencia M. 2009 (3.0)										Small sample pilot study. Data suggest comparable short term efficacy between both groups (kinesiotherapy with stretching vs. myofascial PT)

Dobkin PL, 2005 (3.0)										Poor compliance making conclusions difficult.
Koulil SV, 2011 (3.0)										Waitlist control bias. Data suggest physical fitness improved following CBT.
Koulil SV, 2010 (3.0)										Waitlist control bias. Data suggests CBT and exercise improved pain and fatigue both short and long term.
Burckhardt CS, 1993 (2.5)										Data suggests comparable efficacy between the education and education plus physical training group.

Evidence for Yoga

Author Year (Score):	Category	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results	Conclusion:	Comments:
da Silva, 2007 (score=3.5)										Data suggest similar results between both yoga groups, but the RYT group reported less pain during treatment but over time RY patients reported less pain.

Evidence for Pilates

Atlan, 2009 (score=3.0)										Data suggest pilates group had improved FIQ and pain at week 12.

Evidence for Aquatic Therapy Other than Swimming

Evcik 2008 (3.5)										Randomized open label study. Both groups showed improvement but there were no statistically significant improvement.
Mannerkorpi 2000 (3.5)										Possible randomization failure as NSAID use was significantly lower in treatment program.

Ortega 2010 (3.5)										Small Sample. Data Suggest regular aquatic exercise improved the inflammatory response, which may be deregulated in Fibromyalgia patients.
Tomas-Carus 2007 (2.5)										Data suggest aquatic training group reported improved Q o L measures.

Evidence for Spa and Balneotherapy

Zijlstra, T.R. 2007 3.5										Data suggest temporary benefit from spa therapy but at 1 year, no difference between groups.
Dönmez, A 2005 3.5										Small sample. Usual care bias.
Koçyiğit, B. F. 2016 3.5										Data suggests balneotherapy has positive impact on fibromyalgia patients at day 15, day 30, 3 months and 6 months post intervention.

Neumann L, 2001 3.5										Data suggests balneotherapy improved quality of life in fibromyalgia patients for 3 months on physical measures.
Özkurt S, 2012 3.5										Usual care bias. No table company 2 arms.
Buskila, D 2001 3.5										Both groups showed improvement. Data suggests at 3 months most symptoms associated with fibromyalgia showed sustained improvement in the sulfur bath group.
Eksioglu 2007 (3.5)										Data suggest improvement from combination therapy (stanger bath + amitriptyline)
Fioravanti, A 2007 3.0										Unclear if reported efficacy is due to mud pack or thermal bath.

Bazzichi L. 2013 3.0										Data suggest mud bath better than balneotherapy which may be due to the heat of the mud bath, but both groups showed improvement in symptoms.
Fioravanti, A 2009 3.0										Usual care bias. Treatment not compared to active control.
Kesiktas N, 2011 2.5										Small sample, high dropout rate. Data suggests similar efficacy between all three groups.
Ardiç F, 2007 2.5										Small sample. Data suggests some benefits from balneotherapy.
Evcik 2002 (2.0)										Usual care bias in control group.

Evidence for Whole Body Vibration

Sañundo, B 2012 (score 3.5)	Fibromyalgia	RCT								Data suggests a significant improvement in balance in WBV

										group after 6 weeks.
Sañundo, B 2010 (Score = 3.5)	Fibromyalgia	RCT								Data suggest adding WBV to an exercise program in FM patients improve QOL as reflected in FIQ

Neuropathic Pain

Exercise

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Jordan 2016 (score=2.5)	Exercise	RCT								Non-randomized observational study. Pilot study. Virtual walking may benefit neuropathic pain.

Aerobic Exercise

Dixit 2014 (score=3.5)	Aerobic exercise									Data suggest efficacy at 8 weeks for both a change in MDNS and conduction velocity.
Dixit 2014 (score=3.5)	Aerobic exercise									Data suggest efficacy.

Tricyclics/Tetracyclics

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Max 1988 (score = 3.5)	Tricyclics Amitriptyline vs Lorazepam or Placebo.									Crossover trial data suggest greater number of patients had better pain relief (47 %) with

										amitriptyline vs lorazepam or placebo 15%, 16%.
Kudoh, 2003 (score = 3.5)	Tricyclics Maprotiline									Sparse methods, Data suggest maprotilline increased perception thresholds 2 months post intervention.
Kishore-Kumar 1990 (score = 3.0)	Tricyclics - Desipramine									Crossover design, sparse methods. Data suggest significant pain relief with despiramine from weeks 3 to 6.

SNRIs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Irving, 2014 (score=3.5)	SNRIs Duloxetine									Open label trial. Data suggest comparable efficacy between groups but side effects were drug specific.
Yucel, 2005 (score=3.5)	SNRIs									Sparse methods. Data suggest a

	Venlafaxine									decrease in pain intensity with venlafaxine.
Wernicke, 2006 (score=3.0)	SNRIs Duloxetine									Open label study, routine care bias, and high dropout rate.

Antipsychotics

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Nathan, 1978 (score=2.0)	Chloprothixene									Non-randomized prominent side effects from drug.

Anticonvulsants

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Raskin, 2004 (score=3.5)	Anticonvulsants Topiramate	RCT								Almost 50% dropout rate in treatment arm.

Gabapentin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Jensen, 2012 (score=2.5)	Gastroretentive Gabapentin									Undetermined numbers of completers vs. dropouts. Data suggest

										association between early pain alleviation and treatment response at 10 weeks.
Jensen, 2013 (score=2.5)	Gastroretentive Gabapentin									Open label extension study. Data suggest at 24 weeks; G-GR was well tolerated with small weight gain.

Pregabalin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Irving, 2014 (score=3.5)	Pregabalin									Open label trial. Data suggest comparable efficacy between groups but side effects were drug specific.
Tanenberg 2011 (3.5)	Pregabalin	RCT								Open Label. A non-inferior study which suggest comparable efficacy between duloxetine and gabapentin.
Stacey 2008 (2.5)	Pregabalin	RCT								Open Label Trial. Data suggest pregabalin may be effective those patients who have

										no responded to other common NP pain medications.
Jensen 2012	Pregabalin	Post-hoc analysis								Post-hoc analysis. Data suggest pregabalin improved PQAS to a greater extent them on deep or surface pain from peripheral neuropathy.
Gammaitoni 2013	Pregabalin	Post-hoc analysis								Post-hoc analysis suggesting pre-titration scores reliably predict pregabalin responder in NP patients.

Antivirals

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Galbraith, 1983 (score=2.5)	Antivirals Amantadine									Details are sparse and unclear. Data suggest amantadine may help PHN and decrease lesions time.
Mondelli, 1996 (score=2.0)	Acyclovir									Usual care bias, non-randomized, data suggest oral ACV may reduce motor

										neuritis but does not reduce the incidence of PHN.

Homeopathy and/or Complimentary Medicine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Rajanandh, 2014 (score=3.5)	Compliment ary Medicine Vitamin E									Open label study, Usual care bias. Vitamin E "may" decrease some pain in diabetic neuropathy patients. Data suggest Vitamin E improved pain scores in patients 50 years of age and older.

Acupuncture

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Ursini 2011 (3.0)	Acupuncture	RCT								Nested, open label study, High dropout rate. Many of the randomized patients did not receive the allocated intervention.
Pan 2008 (1.5)	Acupuncture	RCT								Sparse methods. Little data regarding group characteristics.

Electroacupuncture

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Jalali 2006 (2.5)	Electroacupuncture	RCT								Open label trial. Small sample size (n=25). Treatment time varied between participants, but treatment group had positive response to ultraviolet B.
Peng 2012 (2.5)	Electroacupuncture	RCT								Sparse methods. Data suggest accelerated blister healing and lesion resolution in treatment group.

NSAIDS & COX-2 Inhibitors

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Shin, 2013 (score=3.5)	Anti-inflammatories Oral Prostaglandin									Sparse methods, data suggest significant TSS improvement at 8 weeks.

Corticosteroids

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Keczkes, 1980 (score=3.0)	Prednisolone									Data suggest prednisolone reduced the length and incidence of PHN.

Dextromethorphan

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Grace 1998 (score = 8.0)	Dextromethorphan	RCT	Sponsored by Algos Pharmaceuticals. No mention of COI.	N = 37 scheduled for laparotomy for various causes, mostly cancer and inflammatory bowel diseases	Age range 25-75 years. Sex: unknown.	Dextromethorphan (DM) 60mg night before surgery and 1 hour before surgery (n = 18) vs. placebo (n = 19).	4 and 24 hours	Intraoperative morphine use lower in DM group. Total morphine sulfate use trended towards increased use 1st 24 hours. Intraoperative morphine use: dextromethorphan (13.1±1.0) vs. placebo (17.6±1.4), p = 0.012. NS between groups at all other times.	"[T]he preemptive use of 60mg of oral dextromethorphan given the night before and again an hour before surgery reduces intraoperative, but not postoperative, morphine requirements."	Small numbers. Procedures differed between patients. No post-operative differences noted in analgesic use.

Heiskanen 2002 (score = 8.0)	Dextrometh orphan	Crossover Trial	Funded by the Helsinki University Hospital Research Funds (TYH9111). No mention of COI.	N = 20 with chronic pain >6 months	Mean age: 51.5 years; 15 males, 5 females.	Oral dextromethorph an 100mg PO (n = 10) vs. placebo 4 hours prior to IV morphine 15mg (n = 10) (5mg over 2 minutes, then 10mg in 1 hour).	Follow up 1-2 weeks.	No significant differences between groups.	"[O]ral dextromethorphan 100mg had no effect on pain relief by intravenous morphine 15 mg in patients with chronic pain."	Small numbers. All patients received IV morphine. Pain syndromes varied from CLBP to post-stroke central pain.
Nelson, 1997 (score=3.5)	Dextrometh orphon									Crossover trial, small sample, sparse methods, dextramethorph an may reduce DN not PHN.

Immune Modulators (Isoprinosine, Cimetidine)

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Miller, 1989 (score=3.0)	Cimetidine									Data suggest cimetidine may accelerate healing and shorten pain in HZ patients.

Topical Creams

Fuchs, 1998 (score=3.0)	Topical capsaicin, topical EMLA									Non-randomized, very small sample, data suggest lack of efficacy for topical EMLA to reduce the pain associated with topical capsaicin.

Topical Suspensions

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Bareggi, 1998 (score=3.5)	Topical suspension + Oral Medication									Non-randomized, small sample, data suggest topical ASA/diethyl ether was superior to oral ASA as evidenced by an 82.6% decrease in VAS scores vs 15.4%.

Capsaicin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Fuchs, 1998 (score=3.0)	Topical capsaicin, topical EMLA									Non-randomized, very small sample, data suggest lack of efficacy for topical EMLA to reduce the pain associated with topical capsaicin.

Plasters

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Baron 2009b (score=3.5)										Open label multi-center trial. Data suggest comparable efficacy at 4 weeks post treatment but with fewer in complications in lignocaine plaster group.
Baron 2009c (score=3.5)										Open label study. Sparse methods. Data suggest monotherapy non-responders combination

										therapy may provide pain relief.

TENS

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Stepanović 2015 (2.5)	TENS	RCT								Sparse methods. Data suggests TENS better than other groups to help prevent PHN but no group prevented all PHN.

tDCS

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kumru 2012 (3.5)	tDCS	RCT								Non-RCT. Data suggests CHEPs were changed by tDCS + VI.

Evoked Potentials

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kumru 2011 (3.5)	Evoked Potentials	RCT								Experimental non randomized study. Data suggests neuropathic pain in spinal cord injured patients may be associated with alterations in somatosensory pathways.

Scrambler Therapy

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Marineo 2012 (3.0)										Pilot study. Scrambler therapy may benefit chronic neuropathic pain patients more than conventional therapy.

Nerve Blocks

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Xiao, 2014 (score=3.5)										Data suggest single dose of pregabalin better than block

Triamciniolone Acetonite

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Amjad 2005 (3.5)	Triamciniolone Acetonite	RCT								Data suggests Triamciniolone acetonite plus lignocaine better for treatment of PHN than lignocaine alone at both 6 and 12 weeks.

Vitamin B12 & B1

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Talaei, 2009 (score=3.0)	Nortriptyline and Vitamin B12									Data suggest Vitamin B-12 may be better than nortriptyline for treating DN pain.

Systemic Adenosine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Belfrage, 1995 (score=3.5)	Infusion Therapy									Crossover study with 2 infusions per group, small sample with sparse methods. Data suggest adenosine may reduce NP pain but conclusions difficult with only 7 patients.
Lynch, 2003 (score=2.5)	Infusion therapy									Sparse methods, both phase I and phase II are mixed in paper

Guanethidine

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Wahren, 1995 (score=3.5)	IV Therapy									Non-randomized, small sample, data suggest inconclusive long term results from IV guanethidine as differing numbers of treatments in groups.

Intrathecal/Epidural Drugs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Pasqualucci 2000 (Score = 3.0)	Intrathecal & Epidural	RCT								Data suggest methylprednisolone plus local anesthesia better than IV acyclovir and oral prednisolone at 12 months. Cross to Iv acyclovir after putting in epidermal section.

Chronic Electrical Stimulation with implanted Electrodes

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Nuti, 2012 (score=3.5)										Data suggest about ¼ of MCS treated patients reported enhanced motor function.

Dorsal Root Ganglion Destruction via Adriamycin

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Chun-Jing, 2012 (score=3.0)										Approximately same numbers of second procedures in Adriamycin groups vs control group. Both compliance and dropout rate indeterminable.

Spinal Cord Stimulation

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Reddy, 2015 (score=3.5)										Non-RCT, small sample (n=12). Data suggest HFS was preferred by most subjects to low-frequency stimulation (LFS).

Wolter, 2011 (score=3.5)										Small sample size crossover trial. Data suggest sub-threshold stimulation is measurable but not clinically effective.
Duarte, 2016 (score= 3.5)	Spinal cord stimulation	RCT	No sponsorship or COI.	N = 60 with painful diabetic neuropathy	Mean age 59 years: 38 males, 22 females.	Conventional medical practice (CMP) alone (N = 20) Vs Conventiona medical practice supplemented by spinal cord stimulation (SCS) (N = 40)	6 months	The difference in QALYs ($p < 0.001$) Patients randomized to SCS experienced a higher QALY gain when compared to the patients receiving CMP.	"SCS resulted in significant improvement in pain intensity and QoL in patients with PDN, offering further support for SCS as an effective treatment for patients suffering from PDN. From a methodological point of view, different results would have been obtained if QALY calculations were not adjusted for baseline EQ-5D scores, highlighting the need to account for imbalances in baseline QoL."	Standard care bias. Baseline difference in outcome measure. Data suggest improved pain and QOL at 6 months.

Evidence for Back Schools

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Norbye, 2016 (score=3.5)										Wait list control bias. Data suggest similar efficacy at 12 month follow-up between groups for return to work (RTW) between groups with a slight trend toward WL group returning earlier.
Tavafian, 2007 (score=3.5)										No placebo. Both groups received meds. Interventional group reported better quality of life measures at 3, 6, 12mo. Generalizability of study data beyond Iran unclear.
Bendix, 1997 (score=3.0)										Data suggest FR program better than other less intensive programs for improved back pain, already to return to work (improved

										disability) less analgesic use and improved physical activity.
Devasahayam, 2014 (score=3.0)										Small sample (pilot study). High dropout rate. Baseline differences between groups for BMI and VNP.
Paolucci, 2012 (score=2.0)										Small sample size. Conclusions limited due to sparse methods and limited description of sample characteristics.
Pain Management										
Szulc, 2015 (score=3.0)										Standard care control bias. Sparse methods. Data suggest combination MET and McKenzie Method improved pain and disability.

Evidence for Chronic Pain Management Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Dear, 2013 (score=3.5)										Waitlist control bias. Data suggest clinician guided internet-

										delivered CBT maybe useful for managing anxiety disability depression in chronic pain.
Mitchell, 1994 (score=3.5)										Only small differences between treated and control groups. Aerobic exercise components appear weak, possibly contributing to suboptimal results.
Haas, 2005 (score=3.5)										Waitlist control bias. Data suggest no advantage to CDSMP over waitlisted controls for improvement in pain, or self-efficacy, but there was a trend towards improving fatigue, emotional well-being and disability days.
Anderson, 2015 (score=3.5)										Data suggest TPA may be effective in earlier return to work in sick

										listed individuals.
Ruehlman, 2011 (score=2.5)										Wait list control bias. High dropout rate. Data suggest increased knowledge regarding pain in study population as well as a reduction in depression, anxiety, and stress as well as pain outcome measures if the program was utilized.
Brown, 2013 (score=2)										Usual care bias. Data suggest improved perceived pain control in MBPM group.

Evidence for Multidisciplinary Rehabilitation Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
De Buck, 2005 (score=3.5)										Population of chronic rheumatologic diseases. Usual care bias. High dropout rate. Data suggest although the VR

										program did not decrease job loss, mental health and fatigue improved.
Abbasi, 2012 (score=3.5)										Small sample size. Sparse methods.
Martins, 2014 (score=3.5)										Small sample, sparse methods. Data suggest weekly multidisciplinary programs (WIPs) may improve quality of life in patients diagnosed with fibromyalgia syndrome.
Streibelt, 2013 (score= 3.0)										High dropout rate (approximately 50% at 12 months). Baseline differences between groups (depression 90.4 vs 70.5) and current episode of sick leave (74.1 vs 87.5). No pain

										medication history or current use.
Turner-Stokes, 2003 (score=3.0)										Open trial with baseline differences between groups for chronicity of pain (10.26 vs 6.76). At 12 months, combined dropout rate about 33%. No control group nor medication details.
Brendbekken, 2016 (score= 3.0)										At 12 months, both groups had an approximate 40% dropout rate. Pain history and current use not described.
van der Maas, 2016 (score=3.0)										High dropout rate of 45%, usual care bias. Pain medication details not included.
Heutink, 2012 (score=3.0)										Wait list control bias. Medication history and use

										not described. Data suggest anxiety and participation improved in intervention group but not on pain intensity.
Heutink, 2014 (score=3.0)										Follow-up from Heutink 2012. Small sample for long term analysis. CBT may be useful for teaching coping strategies to individuals with chronic pain.
Castell 2013 (score=2.5)										High dropout rate, contact bias in experimental group. Data suggest improved sleep, psychological distress and catastrophizing improved and improvement was maintained at 12 months.

Casaneuva-Fernández (score=2.5)										Data suggest improvement in experimental group in terms of 6 minute walking test, grip strength, social function and vitality.
Toussaint 2012 (score=1.5)										High dropout rate. Standard care bias.

Evidence for Interdisciplinary Pain Rehabilitation Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Olason 2004 (3.5)										No control/reference group. Patients served as their own controls. Data suggest patients returning to work increased from 18.4% to 59.2% post discharge. Data also suggest anxiety and depression treated via CBT decreased and

										analgesics were withdrawn and there was reduced pain.
Martín 2014 (score=3.5)										Sparse methods. High overall dropout rate (39% CG, 64% EG_1) making robust conclusions impossible.
Saral 2016 (score=3.5)										Data suggest comparable efficacy on most FM outcomes.

Evidence for Other Functional Restoration Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Kim, 2015 (3.5)	Functional restoration	RCT	No sponsorship or COI.	53 patients with chronic lower back pain.	Mean age 29.1; No mention of sex.	CORE programme the 30-minute CORE programme, five times per week, for eight weeks, with additional use of hot-packs and transcutaneous electrical nerve stimulation (N = 27) vs Control (N = 26)	2 months	Pain pressure threshold in quadratus lumborum CORE vs Control 1.3 vs 0.1 ($p < 0.001$) Pain pressure threshold in sacroiliac joint 1.2 vs 0.1 ($p < 0.001$)	"The CORE programme is an effective intervention for reducing pain at rest and movement induced pain, and for improving the active range of motion and trunk proprioception in female office workers with chronic low back pain."	High dropout rate. Data suggest intensity of pain during movement was improved.

Monteiro-Junior 2015 (score=3.5)	Functional Restoration	RCT	No mention of sponsorship. No COIs.	N=34 older woman with Low Back Pain (CLBP	Mean age 68 ± 4 years. Females only.	Control Exercise Group did strength exercises and core training (n=14) vs. Experimental Wii Group (n=16).	Pre-post intervention.	Non-significant changes in functional capacity stand up in either group. Mean functional sit changed from 2.3±1.5 pre to 3.3±0.9 post intervention in the Wii group, p=0.04.	"[P]hysical exercises with Nintendo Wii Fit Plus additional to strength and core training were effective only for sitting capacity, but effect size was small."	Data suggest similar results between groups for pain and small advantages to Wii groups for sitting capacity.
Patti, 2014 (3.0)	Functional restoration	RCT	No mention of COI or sponsorship.	N = 38 participants with nonspecific low back pain, who had experienced pain for >12 months	Mean age: 41.48 years, gender: not specified	Intervention in Experimental Group (EG) (n =19) vs Intervention in Control Group (CG) (n =19) The EG completed a 14-week program of Pilates exercises, performed thrice per week under the supervision of an exercise specialist, while the CG was managed with a social program only	T0: immediately prior to the study randomization (baseline) and T1, 14 weeks after T0 (conclusion of the Pilates program)	Posturography measures improved for patients in the EG, with both eyes open and eyes closed (P<0.05). There were no statistical differences in posturography in the CG. ODI decreased significantly in both groups over the 14 weeks of the study protocol: EG, T^0, 13.7 ±5.0 compared with T^1, 6.5±4.0 (P<0.001); and CG, T^0, 10.7 ±7.8 compared with T^1, 8.4±7.8 (P<0.01). A greater extent of reduction in pain was achieved in the EG.	"The Pilates exercise program yielded improvements in pain and posturography outcomes. Our study also confirms the applicability of posturography in evaluating postural instability in patients with NSLBP. Due to our relatively small study group, future studies would be necessary to confirm our findings"	Spare details on baseline characteristics of groups. Data suggest Pilates group (EG) had improved posture and pain.
Gatchel, 2009 (score=3.0)	Functional Restoration	RCT	Sponsored by Congressionally Directed Medical Research Program's Peer	N = 66 military participants with a diagnosed	Mean age: 35.65 years; 44 males, 22 females.	Standard Treatment (medical care with anesthesia pain clinic, N =	Follow-up at baseline, post-intervention, and at 6	Mean Pain Visual Analog Scale score at pre-intervention and post-intervention,	"These results clearly demonstrate the efficacy and military relevance	No details included on pain medications. Data suggest FR

			Review Medical Research Program, and National Institutes of Health. No mention of COI.	musculoskeletal disorder such as CLBP.		36) vs Functional Restoration (N = 30).	months, and 1 year after treatment.	respectfully: Functional restoration 6.1±2.1, 3.8±2.3, Standard treatment 6.1±1.8, 6.0±2.1 (ANOVA p=0.008).	of a FR program for active duty military personnel who have chronic musculoskeletal pain disorders."	group better than standard pain treatment group.
Castro-Sánchez 2016 (score=3.0)	Functional Restoration	RCT	Supported by a grant from a university institution (B). No COI.	N=62 with chronic low back pain.	Mean age 45±7 years. 39 females, 33 males.	Spinal manipulative therapy group or the functional technique group once a week for 3 weeks.	Follow-up 1 month post intervention.	Spinal manipulation showed greater reduction in the RMQ (within groups change score 2.4) vs functional technique therapy (within-groups change score 1.4) at both follow-up periods.	"The results of the current randomized trial showed that three sessions of spinal manipulative therapy did not result in any clinically important short-term benefits over functional technique therapy."	Medication use not described. Data suggest similar results for pain relief in both groups with short term improvement in disability in manipulation group.
Tsauo JY, 2009 (score=2.0)	Functional Restoration	RCT	Sponsored by the National Science Council of the Republic of China. No mention of COI.	N = 25 patients with non-specific low back pain.	Mean age: 47.46 years; 13 males, 12 females.	FCT Group (n=13) – Participants performed warm-up exercise (jogging or walking), a strengthening exercise, work/activity simulation training and fitness and endurance training for 2-3 months. Vs.	Baseline and 3 months (posttreatment).	The Oswestry Disability Index (ODI) pre and post treatment scores in the training group were 22±9 and 16±9 (p<0.05), and in the control group were 13±6 and 13±6, respectively. The change scores for the FCT group were -6.0±8.1 (p<0.05) and for the control group were 0.1±0.3.	"In conclusion, the preliminary results showed an individualised training with trunk stabilisation training programme benefits the chronic LBP patients."	Small pilot sample, high dropout rate. Medication use not available in paper. Data suggest FCT group had improvement in 12 outcome measurements versus only one in control group.

						Control Group (n=12) – participants continued their regular treatment.				

Evidence for Participatory Ergonomic Programs

Author Year (Score):	Category:	Study type:	Conflict of Interest:	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Sharma, 2012 (score=3.0)	Participatory Ergonomics	RCT	No mention of COI or sponsorship.	N = 30 computer workers with chronic neck and upper limb pain and symptoms	No mean age or gender distribution described.	Treatment imposed 5 times each week for 3 weeks. Group A – physical therapy intervention (N = 15) vs. physical therapy with work style intervention (N = 15)	21 days	Mean difference in visual analog scale (VAS) scores for group A and group B respectively: Day 0 5.87±0.22, 6.00±0.20, Day 7 4.00±.02 (p=0.0002 vs Day 0 score), 3.60±0.21 (p=0 0002 vs Day 0 score), Day 21 2.47±0.26 (p=0.0002 vs Day 0 score, p=0.0001 vs Day 7 score), 1.07±0.23 (p=0.0001 vs Day 0 score, p=0.0001 vs Day 7 score). Significance of mean differences in VAS between groups: Day 0 (p=0.6674), Day 7 (p=0.1999), Day 21 (p=0.0001)	"This study provides evidence that both the intervention programs are effective in improving neck and upper limb symptoms in computer workers .but work style intervention with physical therapy intervention is more effective."	Data suggest combination work style intervention with physical therapy more effective for symptom recovery.

Psychological Interventions

Brief Symptom Inventory (BSI)

Evidence for Brief Symptom Inventory (BSI)										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Bruehl, 1996 (Score = 3.5)										Data suggest there may be psychological functional difference between RSD and LBP patients perhaps due to pain location and/or symptomatic medication.
Roth, 2002 (Score = 3.5)										Data suggest there is a relation between educational achievement and chronic pain as lower LOE was associated with less perceived control over pain and higher LOE individuals were more likely to utilize coping strategies.
Tuzer, 2010 (Score = 3.0)										Data suggest no difference between groups regarding causal attributions.
Bair, 2013 (Score = 3.0)										Data suggest depression and anxiety along with chronic pain is strongly associated with increased disability, more severe pain and decrease in HRQL.
Geisser, 1998 (Score = 2.5)										Data suggest the high profile reported more pain disability and display p, poorer psychological functioning.

Multidimensional Pain Inventory (MPI) or Westhaven Yale Multidimensional Pain Inventory

Evidence for Multidimensional Pain Inventory (MPI) or Westhaven Yale Multidimensional Pain Inventory										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Choi, 2013 (Score = 3.5)										Data suggest MPI may successfully distinguish those chronic pain patients regarding additional psychological intervention.
Wilson, 2002 (Score = 3.0)										Data suggest those patients with concomitant chronic pain, depression and insomnia typically report the highest levels of functional improvement but insomnia without depression is associated with increased amounts of pain and distress.

Brief Pain Inventory Short Form

Evidence for Tests of Malingering Memory										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Walton, 2016 (score=3.5)										Data suggest comparable efficacy of 10 item vs 7 item Brief Pain Inventory (BPI).
Keller, 2004 (score=3.5)										Data suggest Brief Pain Inventory (BPI) may be used for pain in noncancer patients, particularly for arthritic pain and LBP.
Ares, 2015										Data suggest Brief Pain Inventory Short Form (BPI-SF) is reliable and valid to measure pain and

(score=3.0)										recall period did not significantly affect scores.
Naegeli, 2015 (score=3.0)										Data suggest Brief Pain Inventory Short Form (BPI-SF) may be used to assess pain in systemic lupus erythematosus (SLE) patients.
Raichle, 2006 (score=3.0)										Self-report data only. Almost 50% of original participants failed to respond.

Tests of Malingering Memory

Evidence for Tests of Malingering Memory										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Test of Malingering Memory (TOMM)										
Greve, 2006 (score=3.0)										Data suggest TOMM may be excluded if another validated forced choice SVT is administrated.

Wechsler Memory Scale III

Evidence for Wechsler Memory Scale III										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Robinson, 2007 (score=3.5)										Data suggest memory and concentration problems more likely an indication of heightened somatic vigilance not poor effort non neuropsychological deficits.

Minnesota Multiphasic Personality Inventory 2 (MMPI-2)

Evidence for Tests of Minnesota Multiphasic Personality Inventory 2 (MMPI-2)										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Diagnoses:	Comparison:	Results:	Conclusion:	Comments:
Duckro, 1985 (score=3.5)										Small sample. Data suggest SLC-90-R subscales for depression and anxiety correlated with several pain measures.

Cognitive Therapy

Cognitive Behavioral Therapy (CBT)										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Vowles, 2011 (score = 3.5)										Data suggest at 3 years post treatment 64.8% of chronic pain patients participating in ACT had functional improvements from baseline.
Carmody, 2013 (score = 3.5)										High dropout rate, sparse methods Data suggest minimal improvements in mental and physical health and some decreased pain & depression as physical health improved catastrophizing decreased.
Shpaner, 2014 (score = 3.5)										Statistically significant differences in pain medication use between groups (CBT 8.8 years vs EDU 5.2 years). Data suggest CBT is associated with changes in resting state functional connectivity.
Berry, 2015 (score = 3.5)										High dropout rate. Waitlist control bias. No significant differences between group outcomes.
Thorn, 2011 (score = 3.5)										Relatively high dropout rate with CBT group requiring additional study participant recruitment. Missing baseline

										group comparison details both groups proved in pain outcomes.
Ang, 2011 (score = 3.5)										Secondary analyses of Ang 2010 small sample , all females data suggest clinical pain correlated with nociceptive responsiveness
Verwoerd 2015 (Score=3.5)										Subgroup (post hoc analysis) of another RCT. Standard care bias. Small sample. Data suggests patients with sciatica and significant kinesiophobia may benefit from PT.
Lazaridou, 2016 (score = 3)										Data suggest CBT may decrease catastrophizing and thus reduce pain.
Fales, 2016 (score = 3.0)										Participant baseline characteristics missing standard care bias data suggest each of efficacy for online CBT for pain management did not result in improved sleep.
Mundt, 2016 (score = 3.0)										Timing was dissimilar between groups. Methods are sparse. Data suggest actigraphy was generally more correlated with PSG than diaries although actigraphy was most sensitive to treatment related changes compared to PSG.
Miró, 2011 (score = 3.0)										Data suggest executive function improvement is related to changes in sleep.
Edinger, 2005 (score = 3.0)										Usual care bias. High dropout rate. Data suggest CBT group reduced nocturnal wake time by 50% and the other two groups experienced only a 20% reduction in nocturnal wake time.
Thieme, 2003 (score = 2.5)										Data suggest improvement in operant pain treatment (OTG) group for pain intensity and decreased pain medications, physician appointments and hospital days.
Koulil, 2011										Waitlist control bias, sparse methods. Data suggest both pain avoidance and

(score = 2.5)										pain persistence treatments improved CB factors.
Vlaeyen, 1996 (score = 2.5)										Waitlist control bias. Data suggest each of efficacy of a highly structured CBT plus group education to enhance pain coping skills.
Williams, 2002 (Score = 2.5)										Standard care control bias, sparse methods Data suggest short term benefits from CBT
Martínez-Valero, 2008 (Score = 2)										Pilot study, small individual group sizes both CBT and CB groups had more contact time with the therapy vs control.
Castel, 2007 (Score = 2.0)										Data suggest hypnosis then analgesia better then hypnosis then relaxation for pain.
Linden, 2014 (Score = 2.0)										Sparse methods, results and data not clearly data suggest CBT may benefit chronic pain patients by increased coping skills.
Garcia, 2006 (Score = 2)										Small samples per group sparse methods. Data suggest immediate post intervention benefits as well as at 3 months with CBT. Also combination CBT treatment was no more effective than CBT alone.
Other Psychological Therapies										
Domenech, 2011 (Score = 3.0)									Data suggest attitudes and beliefs regarding LBP may change where education and training involves both biomedical and biopsychosocial construct.	
Campbell, 2012 (Score = 3.0)									Data suggest changes in catastrophizing may preside and trigger-pain response changes.	
Coppieters, 2016 (score = 2.5)									Crossover design, randomization failure. Population of different types of chronic pain patients.	

Fear Avoidance Belief Training (FABT)

Evidence for Fear Avoidance Belief Training (FABT)										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/ Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Wood, 2008 (Score= 3.0)										Waitlist control bias. High dropout rate. Data suggest a trend in pain disability in the treatment group.
Flink 2016 (Score= 2.5)	Fear Avoidance Belief Training									Waitlist control bias. High dropout rate. Data suggest significant castastrophization correlated to a poor treatment response.

Biofeedback

Evidence for Biofeedback										
Author Year (Score):	Category:	Study type:	Conflict of interest	Sample size:	Age/Sex:	Comparison:	Follow-up:	Results:	Conclusion:	Comments:
Weeks, 2015 (Score = 3.5)										Pilot study, therefore small sample high dropouts.
Buckelew, 1998 (score = 3.5)										Data suggest comparable efficacy between all three groups as all improved self efficacy but combination group maintained benefits for 2 years.
Sarnoch, 1997 (score = 3.0)										Small sample. Non-randomized. Data suggest intensity of pain appears to be associated with lowered baseline EMG activity.

Jensen 2013 (3.0)	Biofeedback	RCT	Sponsored by a research grant from the Craig H. Neilsen foundation. No mention of COI.	N=13 individuals with spinal cord injury induced chronic pain.	Mean age 46.1±12.6; 7 males.	All patients received 12 session of neurofeedback training for three different protocols.	Baseline, post treatment, 3 month follow up.	Worst pain intensity pre vs post treatment (mean±SD): 7.54±1.88 vs 6.75±1.72 (p=0.013). Pain unpleasantness pre vs post treatment (mean±SD): 6.76±2.15 vs 5.80±1.86 (p=0.026). No significant changes between the three different protocols in pain reduction.	"[T]he findings suggest that some individuals with refractory chronic pain associated with spinal cord injury may benefit from NF training. Although the benefits found following 12 sessions of training were small, the majority of the participants were highly satisfied with the intervention.	Small sample. Data suggest NF may be efficacious for SCI-related pain.
Hassett 2007 (2.0)	Biofeedback	Case series	No mention of sponsorship or COI.	N=12 women affected by Fibromyalgia.	Mean age 38.5±12.5; 12 females.	All patients received 10 trials of Heart rate variability biofeedback.	Baseline, session 10, and 3 months.	Fibromyalgia Impact Questionnaire / Beck Depression Index II / McGill Pain Questionnaire / score baseline vs 3 month (mean±SD): 55.5±18.4 vs 41.9±19.5	"These data suggest that HRV biofeedback may be helpful as a treatment for FM. The major findings of this study indicate that a ten session trial of HRV	Non-RCT using a small convenience sample with no comparison group. A trend towards pain improvement

								(p=0.0022) / 21.7±12.3 vs 15.5±12.1 (p=0.0055) / 25.1±8.9 vs 21.1±16.2 (p=0.0060).	biofeedback significantly improved overall functioning and depression in patients with FM."	
Neblett 2010 (2.0)	Biodfeedback	RCT	No mention of sponsorship or COI.	N=140 patients with chronic lumbar pain. N=30 control patients.	Group 1: Mean age 44.3±10.0; 60 males. Group 2: Mean age 42.7±10.1; 26 males. Group 3: Mean age 37.6±9.3; 16 males.	Group 1: received surface electromyography (SEMG) biofeedback to assist in stretching and relieve fear of pain as well as muscle relaxation until flexion relaxation was achieved. (n=104) vs. Group 2: received functional restoration training which included intensive interdisciplinary programming to restore function 2-5 days per week over 2 or more months (160-240 hours), (n=36) Group 3:	Baseline and post treatment.	Group 1 vs group 2, post treatment number participants whom achieved relaxation flexion (n %): 61 (86%) vs 6 (26%). Group 1 vs group 2, post treatment mean SEMG/ Gross lumbar flexion/ pelvic flexion (Mean±SD) : 3.3±4.1 vs 11.8±10.7 (p=0.000) /109.7±13.0 vs 94.4±19.7 (p=0.000) / 58.0±15.2 vs	"Although standard functional restoration treatment of CLBP subjects is effective for increasing lumbar flexion ROM and for improving MVF SEMG levels, the addition of a SEMGAS biofeedback training protocol can result in normalization of the flexion-relaxation phenomenon, so that these subjects are comparable to a pain free control group."	High dropout rate especially in SEMG group with baseline comparability differences between groups.

						asymptomatic colleagues w/ no history of back pain.		46.1±46.1 (p=0.002). Group 1 vs Group 3, post treatment Max voluntary flexion (MVF), range of motion (ROM), SEMG: no significant difference. Group 2 was significantly worse in mean SEMG, ROM, and MVF vs group 3 post treatment.		
Tan, 2014 (score = 2.0)										High dropout rate. Data suggest self-hypnosis with audio recording may be as effective as professionally administered hypnosis.

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