AMERICAN COLLEGE OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE

Chronic Pain Guideline

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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]

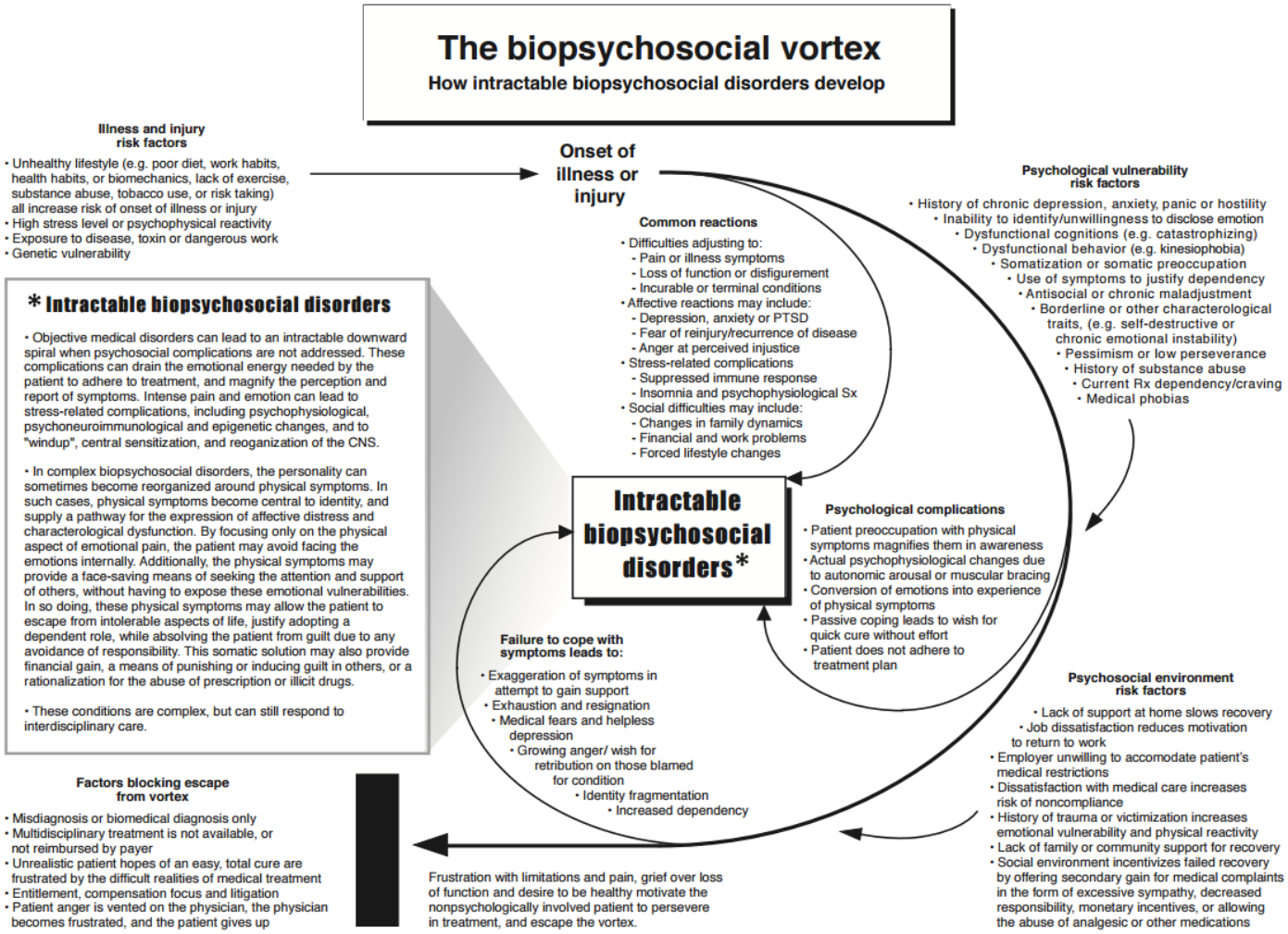

Figure 1. The biopsychosocial vortex: How intractable biopsychosocial disorders develop. Reprinted with permission from Daniel Bruns, PsyD, and John Mark Disorbio, EdD.[1]

[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. Red Flags for Potentially Serious Conditions Associated with Chronic Pain*). 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 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)	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) New findings at a distant site to the original complaints

Disorder	Medical History	Physical Examination
Infection	Constitutional symptoms, such as recent fever, chills, or unexplained weight loss Recent bacterial infection (e.g., urinary tract infection); I.V. 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)

Disorder	Medical History	Physical Examination
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: Interval Pain History).

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?

[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.

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?
   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. "Nonphysiologic" Physical Examination Signs [43]). 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
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

[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.

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 patients' 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 and Definitions). 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 reflex abnormalities, neurotrophic skin changes	EMG/NCS Glucose tolerance testing, fasting glucose and/or hemoglobin A1c if concerns about diabetes mellitus 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)

Probable Diagnosis or Injury	Symptoms	Signs	Tests and Results
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 ≥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

Probable Diagnosis or Injury	Symptoms	Signs	Tests and Results
Chronic Pain Syndrome**	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), passive-dependence	Psychological evaluation (including diagnostic testing as indicated) may be useful

*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, 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 Issues). 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)
- Tender Points (see Fibromyalgia)
- 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
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.

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.

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. Adverse Effects of Injections).
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

Complications	Details
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 – **No Recommendation, Insuffcient 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 Q.I.D. 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 B.I.D. dosing over the 60mg Q.D. 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 – **Not Recommended, 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 – **Not Recommended, 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 – **Not Recommended, 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 – **Not Recommended, 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 – **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 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 – **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 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

No Recommendation.

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 – **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 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 – **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 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)
- Tender points (see Fibromyalgia)
- 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.

Diagnosis

Symptoms and Signs

- Constant severe burning or throbbing pain typically isolated to in one limb

[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.

- 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. Diagnostic Criteria for CRPS for Clinical Purposes*)[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.

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.

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. Adverse Effects of Injections**).**
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

Complications	Details
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

No Recommendation.

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.

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.

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.

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.

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 Q.I.D. 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 I.V. 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 I.V. parecoxib B.I.D. 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.

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 Q.D. There appears to be either a minimal or no advantage of the B.I.D. dosing over the 60mg Q.D. 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). 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 Q.D. x 2 days, then 600mg B.I.D. x 2 days, then 600mg T.I.D. 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.

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 Q.D. for 8 weeks; Clodronate 300mg I.V. Q.D. for 10 days; Alendronate 7.5mg I.V. Q.D. for 3 days; Pamidronate 60mg I.V. for one dose; Neridronate 100-mg I.V. 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.

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 T.I.D. for 3 weeks [354], 400IU Q.D. for 4 weeks [355], and 200 IU Q.D. 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.

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 I.V. 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.

Intravenous Regional Anesthesia with Clonidine for Preventive Administration Prior to Surgery

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:	I.V. 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.

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 P.O. Q.D. for 14 days and then 10 mg/week taper [341]. A second regimen was prednisone 10mg P.O. T.I.D. 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.

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.

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.

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.

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.

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 P.O. T.I.D. 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.

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. I.V. 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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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: a CRPS Patient*	See Table 9. Selection Criteria for Implantable Spinal Cord Stimulator in
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. Selection Criteria for Implantable Spinal Cord Stimulator in a CRPS Patient*). 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. Psychological And Biopsychosocial Assessment Tools). (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.

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 and Psychological Interventions
Rehabilitation for Delayed Recovery for Fibromyalgia ..... See Behavioral and Psychological Interventions
Biofeedback for Fibromyalgia ..... See Behavioral and Psychological Interventions
Relaxation & Meditation Training for Fibromyalgia ..... See Behavioral and Psychological Interventions
Functional Restoration for Fibromyalgia ..... See Behavioral and Psychological Interventions
Work Conditioning, Work Hardening, and Early Intervention Programs for Fibromyalgia ..... See Behavioral and Psychological Interventions
Interdisciplinary Pain Rehabilitation Programs for Fibromyalgia ..... See Behavioral and Psychological Interventions
Other "Ad Hoc" Functional Restoration for Fibromyalgia ..... See Behavioral and Psychological Interventions

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 Avoidance Belief Training for Fibromyalgia).

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**

Probable Diagnosis or Injury	Symptoms	Signs	Tests and Results
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

TABLE 10. CONTINUATION

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. Adverse Effects of Injections.

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

Complications	Details
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.

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

No Recommendation.

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 Q.I.D. 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 Q.D.-B.I.D., although there appears to be either a minimal or no advantage of the B.I.D. dosing over the 60mg Q.D. 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 Q.D. [751, 752] and 120mg P.O. Q.D. [701, 752] Milnacipran 50mg B.I.D. to 100mg B.I.D. (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 I.V. 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 I.V., 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 B.I.D. for 1 week, then 1,200mg/day for 2 weeks, then 600mg T.I.D. for 2 weeks, then 600mg B.I.D., 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 P.O. Q.D. [779, 780], with an initial dose prescribed of 150mg P.O. Q.D. 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 Q.D. 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 I.V., 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 I.V. 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 Recommendation, 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.

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, 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. Group 1 IARC Carcinogens with Sufficient Evidence of Causing Lung Cancer in Humans And Primary Type of Exposure). 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

Agent	Primary Exposure Type
• 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 **Complex Regional Pain Syndrome**.

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 – **Strongly Recommended, Evidence (A)**
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. Adverse Effects of Injections).

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

Complications	Details
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 Q.I.D. 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 B.I.D. [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 B.I.D. [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 I.V., 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 T.I.D. 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% T.I.D. to Q.I.D. 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

No Recommendation.

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

No Recommendation.

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

No Recommendation.

There is no recommendation for or against ketamine infusion for treatment of neuropathic pain.

Strength of Evidence – **No Recommendation, 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 intrathecal 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.

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)

Tertiary Pain Programs: Interdisciplinary Pain Rehabilitation Programs, Multidisciplinary Rehabilitation Programs, Chronic Pain Management Programs, and Functional Restoration Programs ..... Recommended, Evidence (C)

Participatory Ergonomics Programs for Patients with Chronic Pain ..... 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.*

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

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. Psychological And Biopsychosocial Assessment Tools 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]*

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. Differences between psychological screening and assessment).
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. Differences between psychological screening and assessment).

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. Differences between psychological screening and assessment).
    - **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 A4). 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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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/uploads/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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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 (QoI), 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.

Assessment Task	Test	Description
	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

Test Acronym Length Reading Level	Description
BSI 18 **3-5 minutes** **6th grade**	**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 *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

Test Acronym Length Reading Level	Description
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

Assessment Task	Test	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**, below**
	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

Assessment Task	Test	Description
Comprehensive Chronic Pain Psychological Assessment		***These are standardized biopsychosocial psychological tests.***
		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

Assessment Task	Test	Description
	MBMD **20-30 minutes** **6th grade**	**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 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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
	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.

Assessment Task	Test	Description
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

Assessment Task	Test	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.

Assessment Task	Test	Description
	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.

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