

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Part 1: Introduction

The chronic pain medical treatment guidelines apply when the patient has chronic pain as determined by following the clinical topics section of the Medical Treatment Utilization Schedule (MTUS). In following the clinical topics section, the physician begins with an assessment of the presenting complaint and a determination as to whether there is a “red flag for a potentially serious condition” which would trigger an immediate intervention. Upon ruling out a potentially serious condition, conservative management is provided. If the complaint persists, the physician needs to reconsider the diagnosis and decide whether a specialist evaluation is necessary. If the patient continues to have pain that persists beyond the anticipated time of healing, without plans for curative treatment, such as surgical options, the chronic pain medical treatment guidelines apply. This provides a framework to manage all chronic pain conditions, even when the injury is not addressed in the clinical topics section of the MTUS.

The chronic pain medical treatment guidelines consist of two parts. Part 1 is the introduction. Part 2 consists of pain interventions and treatments. With a few exceptions, Part 2 is primarily an adaptation of evidence-based treatment guidelines, from the Work Loss Data Institute’s Official Disability Guidelines (ODG) Treatment in Workers’ Comp – Chapter on Pain (Chronic). The version adapted is dated October 23, 2008, and it is being adapted with permission from the ODG publisher. Any section not adapted directly from ODG is labeled “[DWC]”.

### Definitions:

Chronic Pain: Chronic pain is defined as “*any pain that persists beyond the anticipated time of healing.*”

Types of Pain: Pain mechanisms can be broadly categorized as nociceptive or neuropathic.

Nociceptive pain: Nociceptive pain is the pain caused by activation of nociceptors, which are sensory neurons found throughout the body. A nociceptor is “a receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged.”

Neuropathic Pain: Neuropathic pain is “pain initiated or caused by a primary lesion or dysfunction of the nervous system.” Normal nociception would not be considered dysfunction of the nervous system.

### Overview

Chronic pain has a huge impact on the individual and society as a whole. It is the primary reason for delayed recovery and costs in the workers’ compensation system. Most chronic pain problems start with an acute nociceptive pain episode. Therefore, effective early care is paramount in managing chronic pain. Given the importance of pain in healthcare, it is presently the subject of intensive scientific research which in turn has generated a growing evidence base regarding the diagnosis, treatment and management of painful conditions.

The International Association for the Study of Pain (IASP) states that pain is “*an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*” (Merskey and Bogduk 1994) This describes pain as a subjective experience; therefore, unlike hypertension or diabetes, there is no objective measurement for pain intensity. Analysis of the objective

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data (psychosocial assessment, physical exam findings, imaging results, lab tests) is needed to evaluate the patient's subjective report of pain.

The experience of pain is a complex phenomenon. Multiple models have evolved over time to explain it. Traditionally, the biomedical model explains pain through etiologic factors (e.g., injury) or disease whose pathophysiology results in pain. It is now understood that this classic biomedical approach to understanding and treating pain is incomplete. Its exclusive application can result in unrealistic expectations on the part of the physician and patient, inadequate pain relief, and excessive disability in those with pain that persists well after the original injury has healed.

The biopsychosocial model of pain instead recognizes that pain is ultimately the result of the pathophysiology plus the psychological state, cultural background/belief system, and relationship/interactions with the environment (workplace, home, disability system, and health care providers). Current research is investigating the neurobiological causes for persistent pain and how structural and functional changes in the central nervous system may serve to amplify and maintain the experience and disability of certain pain condition. (Siddall and Cousins 2007) This is an area of intensive research which will contribute to the scientific evidence base in years to come.

## Pain Mechanisms

Within the biomedical model, pain mechanisms are broadly categorized as nociceptive or neuropathic. Inflammatory mechanisms may also play a role. While there are similarities, each mechanism has unique features and characteristics. This mechanistic approach may provide greater insight into appropriate therapeutic strategies.

Several reviews have detailed the mechanisms and mediators of pain and the components of the ascending and descending pain pathways. In nociceptive pain, signal transduction in nociceptor somatosensory afferent terminals converts mechanical, electrical, thermal, or chemical energy into an action potential which is transmitted to the dorsal horn of the spinal cord by specialized nerve fibers. The signal is then transmitted through ascending cortical pathways to the brain. Nociceptive signals within the brain are sent to two major areas: the somatosensory cortex, where the sensory component of pain is represented in the brain, and the limbic forebrain system, which is the neural substrate for the emotional component of pain experience responsible for feelings of suffering.

Since these areas of the brain interact with other areas of the brain, past memories, external environmental factors, and internal cognitive factors (i.e., psychosocial factors) influence or modulate the pain experience. How the brain integrates all the input is, in part, the basis for the biopsychosocial approach to the management of pain.

Neuropathic pain is “pain initiated or caused by a primary lesion or dysfunction of the nervous system.” (Turk and Okifuji 2001) The altered modulation of the pain response in patients with neuropathic pain causes a state of hyperexcitability and continuous pain signal output in the absence of peripheral tissue damage. “Neuropathic pain can result from injury or trauma (e.g., surgery), infection (e.g., post herpetic neuralgia), endocrine (e.g., diabetes, hypothyroidism), demyelination (e.g., multiple sclerosis), errors in metabolism, neurodegenerative disorders (e.g., Parkinson's disease), or damage directly to the spinal cord or brain (e.g., thalamic stroke).” (Backonja in Loeser, 2001)” (Mackey and Maeda 2004)

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Neuropathic pain is characterized by symptoms such as lancinating, electric shock-like, paroxysmal, tingling, numbing, and burning sensations that are distinct from nociceptive pain.

Many neuropathic pain states have traditionally been thought of as having a primary peripheral etiology. Recent investigation, however, using functional neuroimaging techniques, demonstrates that many neuropathic and other chronic pain conditions may have a large centralized component (central vs. peripheral model). These conditions include, but are not limited to, chronic low back pain (CLBP), fibromyalgia, irritable bowel syndrome, and Complex Regional Pain Syndrome (CRPS)/Reflex Sympathetic Dystrophy (RSD). (Mackey and Maeda 2004)

Inflammation can play a significant role in both nociceptive and neuropathic pain. Inflammation occurs when cells and tissue are damaged and release chemical mediators, commonly referred to as “the inflammatory soup,” that not only induce an inflammatory response but also sensitize nociceptors and other somatosensory components of the nervous system. Peripheral sensitization occurs when inflammatory mediators cause a reduction in the threshold required for nociceptor activation. A similar short-term central sensitization can occur in which there is an increase in neuronal excitability and responsiveness in the dorsal horn. In central sensitization, chemical mediators for inflammation can also upregulate the expression of genes that alter synaptic transmission.

Because of neuronal plasticity, current research is showing that protracted central sensitization (neuronal hyperexcitability) can result in long-term changes that may be important in the transition from acute to chronic pain and the development of chronic pain syndromes. Patients with these syndromes generally have severe and persistent pain that is disproportionate to the tissue injury.

## Models

Models are the conceptual framework to understand pain and serve to establish parameters for reasonable outcomes and acceptable standards of care. These are helpful for physicians, patients, families, healthcare providers, carriers, and compensation systems. Several different models of pain have developed over time, each with strengths and weaknesses.

### Acute vs. Chronic Pain Model

In many situations, acute pain serves as a highly adaptive and beneficial experience. Fundamentally, it serves as a protective warning of actual or impending tissue damage. Acute musculoskeletal pain is a common example in the injured worker and is often a signal of real or impending tissue damage.

Most acute pain is self-limited and may respond to short term administration of analgesics and conservative therapies. However, continued activation of nociceptors with less than adequate pain control can lead to peripheral and central sensitization, a risk factor for persistent pain with prolonged disability, delayed return to baseline function, and delayed return to work.

Chronic pain can be distinguished from acute pain by more than just the time course. Whereas acute pain serves as a protective warning signal, chronic pain has no known survival benefit. Evidence suggests that generation and subsequent maintenance of chronic pain, as opposed to acute pain, may

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involve changes in central pain processing mediated through mechanisms of neural plasticity and ultimately leading to hyper-excitability of central structures in the spinal cord and brain. To complicate matters, unremitting pain may be associated with depression and/or anxiety.

As a practical matter, it is noted that “[t]he distinction between acute and chronic pain is somewhat arbitrary” and “[c]hronicity may be reached from one to six months postinjury.” ACOEM recognizes that the most clinically useful definition might be “chronic pain persists beyond the usual course of healing of an acute disease or beyond a reasonable time for an injury to heal.” (ACOEM Medical Treatment Guidelines Chapter 6 page 108.) The Division of Workers’ Compensation definition of chronic pain, “any pain that persists beyond the anticipated time of healing,” is derived from Bonica’s Management of Pain (Turk and Okifuji, 2001). Therefore, it is a clinical decision to recognize chronicity or persistence of pain when 1) the condition is not improving over time, 2) fails to improve with treatments directed to the specific injured body part (see Clinical Topics section of the MTUS), or 3) in the absence of a specifically correctable anatomic lesion (see Clinical Topics section of the MTUS). Often it takes a number of months for the clinician to recognize when pain becomes chronic.

## Illness Behavior Model

As previously stated pain is a subjective experience, influenced and modulated by cognitive, emotional, and environmental elements. Psychosocial factors can affect the perception and expression of pain. These might include, but are not limited to, a tendency toward anxiety, depression, somatization, fear avoidance, emotional lability, catastrophizing, job dissatisfaction and embellishment.

Further, while frank malingering is rare, secondary gain factors, such as disability income and avoidance of perceived unpleasant tasks can impact the overall clinical presentation. Taken together, psychosocial factors may play a larger role in eventual patient outcome than obvious somatic factors as determined by the nature and extent of the original injury. Efforts directed solely to the management of possible pain generators without addressing psychosocial factors may result in a suboptimal outcome.

## Biomedical vs. Biopsychosocial Model

The traditional biomedical model “assumes disease to be fully accounted for by deviations from the norm of measurable biological (somatic) variables” (Engel 1977). Thus there is always a direct causal relationship between a specific pathophysiologic process and the presence and extent of a particular symptom. While this model has served the medical community well in the treatment and cure of certain diseases (e.g. infectious diseases), it has generally failed in the treatment of chronic illness including persistent pain. For example, for decades there has been an approach to identify the “pain generator” and remove it by cutting it out or blocking it.

In 1977 Engel proposed an alternative, the biopsychosocial model, which focuses greater attention on the patient, rather than presumed pathophysiology. The biopsychosocial model approaches pain and disability as a complex interplay of biological, psychological and social factors. These psychosocial factors can be easily assessed.

The following chart contrasts these two pain models (Hanson and Gerber 1993):

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## Pain Models

<b>Biomedical model</b>	<b>Biopsychosocial model</b>
Most appropriate for acute pain conditions	More useful for those with chronic pain conditions
Emphasizes peripheral nociception	Recognizes the role that central mechanisms play in modulating peripheral nociception or generating the experience of pain in the absence of nociception
Focus on physical disease mechanisms	Recognizes the importance of illness behavior including cognitive and emotional responses to pain
Reductionistic approach to understanding and treating pain	Multidimensional systems approach to understanding and treating pain
Reliance on medical management approaches	Utilization of self-management approaches

Linton identified strong evidence that psychosocial variables are strongly linked to the transition from acute to chronic pain disability and that psychosocial variables generally have more impact than biomedical or biomechanical factors on back pain disability. (Linton 2000) Thus, when clinical progress is insufficient, the clinician should always be prepared to address confounding psychosocial variables, in a coordinated, multidisciplinary manner.

### Medical vs. Self-Management Model

Understandably, patients want their chronic pain “cured” or eliminated. Unfortunately, there are presently no definitive cures for the majority of persistent pain problems, such as axial spine pain, peripheral neuropathies, fibromyalgia, etc. As is the case with all chronic medical conditions, chronic pain must be managed, not cured. In the medical model, responsibility resides primarily with the physician. The self-management approach places primary responsibility on the person with chronic pain. Currently, self-management strategies can significantly improve a patient’s function and quality of life, while reducing subjective experiences of pain. It is important to educate patients on this distinction, to avoid persistent and unrealistic expectations for an elusive cure, where none exists. This unrealistic curative view, often unwittingly fostered by healthcare providers or others, predictably leads to repeated failures, delayed recovery, and unnecessary disability and costs.

### **Risk Stratification**

#### Importance of early identification

Patients not responding to initial or subacute management (see Clinical Topics Section MTUS) or those thought to be at risk for delayed recovery should be identified as early as possible. Simple screening questionnaires may be used early in the clinical course to identify those at risk for delayed recovery. Those at risk should be aggressively managed to avoid ineffective therapeutic efforts and needless disability. Factors that help identify at-risk patients include: (1) those unresponsive to conservative therapies demonstrated to be effective for specific diagnoses; (2) significant psychosocial factors negatively impacting recovery; (3) loss of employment or prolonged absence from work; (4) previous history of delayed recovery or rehabilitation; (5) lack of employer support to accommodate patient

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needs; and (6) a history of childhood abuse (verbal, physical, mental). Of these factors, lost time from work has the highest value in predicting those patients who will experience delayed recovery.

## Subacute Delayed Recovery

Complaints of pain are the most common obstacle to return to work. Undertreatment of pain and/or unrealistic expectations may play a role in delayed recovery. However, the subacute phase is a critical time for the injured worker, as additional time away from work may result in adverse medical, familial, economic, and psychological consequences (including overtreatment, depression and/or anxiety, which can exacerbate pain complaints). When the physician recognizes that the problem is persisting beyond the anticipated time of tissue healing, the working diagnosis and treatment plan should be reconsidered, and psychosocial risk factors should be identified and addressed. If necessary, patients should be directed toward resources capable of addressing medical and psychosocial barriers to recovery.

## Patients with Intractable Pain

Studies have shown that the longer a patient remains out of work the less likely he/she is to return. Similarly, the longer a patient suffers from chronic pain the less likely treatment, including a comprehensive functional restoration multidisciplinary pain program, will be effective. Nevertheless, if a patient is prepared to make the effort, an evaluation for admission for treatment in a multidisciplinary treatment program should be considered.

A patient suffering from severe intractable pain who does not qualify for participation in a chronic pain program or who has failed a chronic pain program “should have access to proper treatment of his or her pain.” California Health and Safety Code section 124960

## **Assessment Approaches**

### History and Physical Examination

Thorough history taking is always important in clinical assessment and treatment planning for the patient with chronic pain, and includes a review of medical records. Clinical recovery may be dependent upon identifying and addressing previously unknown or undocumented medical and/or psychosocial issues. A thorough physical examination is also important to establish/confirm diagnoses and to observe/understand pain behavior. The history and physical examination also serves to establish reassurance and patient confidence. Diagnostic studies should be ordered in this context and not simply for screening purposes.

If a diagnostic workup is indicated and it does not reveal a clinically significant contraindication, the physician should encourage the patient to engage in an active rehabilitation program. Effective treatment of the chronic pain patient requires familiarity with patient-specific past diagnoses, treatment failures/successes, persistent complaints and confounding psychosocial variables (e.g., history of abuse, anxiety, depression, fear-based avoidance of activity, catastrophizing, self-medication with alcohol or other drugs, patient/family expectations, medical-legal/claims management issues, and employer/supervisor/worksites).

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## Evaluation of Psychosocial Factors

For patients with a complex presentation, psychosocial factors have proven better predictors of chronicity than clinical findings. Such variables/factors can and should be assessed.

## **Functional Restoration Approach to Chronic Pain Management**

Many injured workers require little treatment, and their pain will be self-limited. Others will have persistent pain, but can be managed with straightforward interventions and do not require complex treatment. However, for patients with more complex or refractory problems, a comprehensive multidisciplinary approach to pain management that is individualized, functionally oriented (not pain oriented), and goal-specific has been found to be the most effective treatment approach. (Flor, Fydrich et al. 1992; Guzman, Esmail et al. 2001; Gatchel and Bruga 2005)

Functional restoration is an established treatment approach that aims to minimize the residual complaints and disability resulting from acute and/or chronic medical conditions. Functional restoration can be considered if there is a delay in return to work or a prolonged period of inactivity according to ACOEM Practice Guidelines, 2<sup>nd</sup> Edition, page 92. Functional restoration is the process by which the individual acquires the skills, knowledge and behavioral change necessary to avoid preventable complications and assume or re-assume primary responsibility (“locus of control”) for his/her physical and emotional well-being post injury. The individual thereby maximizes functional independence and pursuit of vocational and avocational goals, as measured by functional improvement (see 8 CCR § 9792.20 (f)).

Independent self-management is the long-term goal of all forms of functional restoration. The process and principles of functional restoration can be applied by a physician or a well integrated interdisciplinary team to a full range of problems that include acute injuries (e.g., sports, occupational), catastrophic injuries (e.g., brain and spinal cord injury), and chronic conditions (e.g., chronic pain, multiple sclerosis, etc.) and is the basis for medical rehabilitation and disability management. The principles of functional restoration apply to all conditions in general, and are not limited to injuries or pain.

Multiple treatment modalities, (pharmacologic, interventional, psychosocial/behavioral, cognitive, and physical/occupational therapies) are most effectively used when undertaken within a coordinated, goal-oriented, functional restoration approach (see Part 2).

Using medications in the treatment of pain requires a thorough understanding of the mechanism underlying the pain as well as to identify comorbidities that might predict an adverse outcome. As stated on page 47 of the ACOEM Practice Guidelines, “[c]onsideration of comorbid conditions, side effects, cost, and efficacy of medication versus physical methods and provider and patient preferences should guide the physician’s choice of recommendations.” Choice of pharmacotherapy must be based on the type of pain to be treated and there may be more than one pain mechanism involved. The physician should tailor medications and dosages to the individual taking into consideration patient-specific variables such as comorbidities, other medications, and allergies. The physician should be knowledgeable regarding prescribing information and adjust the dosing to the individual patient. If the physician prescribes a medication for an indication not in the approved FDA labeling, he or she has the

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responsibility to be well informed about the medication and that its use is scientific and evidence-based. When effective, medications provide a degree of analgesia that permits the patients to engage in rehabilitation, improvement of activities of daily living, or return to work. There are no drugs that have been proven to reverse, cure, or “heal” chronic pain. Periodic review of the ongoing chronic pain treatment plan for the injured worker is essential according to the Medical Board of California Pain Guidelines for controlled substances.

When choosing an invasive procedure to treat a specific chronic pain problem, a complex judgment is necessary to make sure that the desired and expected outcome is worth the risk involved, depending on the procedure and individual risk factors.

Please refer to Part 2 to find specific guidelines on chronic pain treatments that include pharmacotherapy, invasive pain procedures, psychological and behavioral therapies, physical and occupational therapies, and other approaches. Selection of treatment must be tailored for the individual case. Whether the treatment is provided by an individual provider, a multidisciplinary group of providers, or tightly integrated interdisciplinary pain program, it is important to design a treatment plan that explains the purpose of each component of the treatment. Furthermore, demonstration of functional improvement is necessary at various milestones in the functional restoration program in order to justify continued treatment.

## **Pain Outcomes and Endpoints**

Pain is subjective. It cannot be readily validated or objectively measured (AMA Guides, 5<sup>th</sup> Edition, page 566). Furthermore subjective reports of pain severity may not correlate well with its functional impact. Thus, it is essential to understand the extent that function is impeded by pain (AMA Guides, 5<sup>th</sup> Edition, page 578).

The physician treating in the workers’ compensation system must be aware that just because an injured worker has reached a permanent and stationary status or maximal medical improvement does not mean that they are no longer entitled to future medical care. The physician should periodically review the course of treatment of the patient and any new information about the etiology of the pain or the patient's state of health. Continuation or modification of pain management depends on the physician’s evaluation of progress toward treatment objectives. If the patient's progress is unsatisfactory, the physician should assess the appropriateness of continued use of the current treatment plan and consider the use of other therapeutic modalities. When prescribing controlled substances for pain, satisfactory response to treatment may be indicated by the patient's decreased pain, increased level of function, or improved quality of life. ([http://www.medbd.ca.gov/pain\\_guidelines.html](http://www.medbd.ca.gov/pain_guidelines.html)).

Additionally, fluctuations are likely to occur in the natural history of patients with chronic pain. Exacerbations and “breakthrough” pain may occur during the chronic clinical course and adjustments to the treatment will be necessary.

## **Conclusion**

We now have an appreciation that chronic pain is associated with structural and functional changes of the peripheral and central nervous system. These changes can lead to the generation and maintenance of

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chronic pain conditions with its associated disability. While biologic mechanisms play a role in the perception of pain, it is also important to recognize that psychological and environmental factors are important. Recognition of these factors will allow the physician to better (1) treat the recently injured patient, (2) identify the “at risk” patient, and (3) refer the patient with intractable chronic pain to the appropriate resources. A full assessment of the patient is required to determine the best approach in any given case.

Therapy for chronic pain ranges from single modality approaches for the straightforward patient to comprehensive interdisciplinary care for the more challenging patient. Therapeutic components such as pharmacologic, interventional, psychological and physical have been found to be most effective when performed in an integrated manner. All therapies are focused on the goal of functional restoration rather than merely the elimination of pain and assessment of treatment efficacy is accomplished by reporting functional improvement. Typically, with increased function comes a perceived reduction in pain and increased perception of its control. This ultimately leads to an improvement in the patient’s quality of life and a reduction of pain’s impact on society.

## References

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**Part 2 – Pain Interventions and Treatments:** All of the following (listed alphabetically) treatment recommendations are adapted from ODG except those labeled “[DWC]”. For those individual treatment guideline topics where the frequency, duration and intensity of the treatment is not addressed, the following principles apply as set forth in the Introduction of these guidelines. Duration of the treatment shall be consistent with the definition of chronic pain as set forth in Section 9792.20(c) and page 1 of these guidelines, and the treatment shall be provided as long as the pain persists beyond the anticipated time of healing and throughout the duration of the chronic pain condition. The duration of continued medication treatment for chronic pain depends on the physician’s evaluation of progress toward treatment objectives, efficacy, and side effects as set forth in the Introduction of these guidelines at page 8. With regard to the frequency and intensity requirements, the treating physician is required, as stated in the Introduction of these guidelines at page 7, to exercise clinical judgment by “tailor[ing] medications and dosages to the individual taking into consideration patient-specific variables such as comorbidities, other medications, and allergies.” The physician shall be “knowledgeable regarding prescribing information and adjust the dosing [i.e. how often {frequency} and how much {intensity}] to the individual patient” as stated in these guidelines at page 7 of the Introduction. Clinical judgment shall be applied to determine frequency and intensity and “[s]election of treatment must be tailored for the individual case” as stated in the Introduction of these guidelines at page 8.

## **Acetaminophen (APAP)**

Recommended for treatment of chronic pain & acute exacerbations of chronic pain. With new information questioning the use of NSAIDs, acetaminophen should be recommended on a case-by-case basis. The side effect profile of NSAIDs may have been minimized in systematic reviews due to the short duration of trials. On the other hand, it now appears that acetaminophen may produce hypertension, a risk similar to that found for NSAIDs.

*Osteoarthritis (hip, knee, and hand):* Recommended as an initial treatment for mild to moderate pain, in particular, for those with gastrointestinal, cardiovascular and renovascular risk factors. (Laine, 2008) If pain is inadequately treated or there is evidence of inflammation, alternate pharmacologic treatment should be considered. In patients with moderate to severe disease, initial treatment with an NSAID may be warranted. The decision to use either class of drugs should be made on a case-by-case basis, incorporating factors including side effect profile and patient preferences. Current guidelines note that evidence is limited to make an initial recommendation with acetaminophen, and that NSAIDs may be more efficacious for treatment. In terms of treatment of the hand it should be noted that there are no placebo trials of efficacy and recommendations have been extrapolated from other joints. (Zhang, 2007) The selection of acetaminophen as a first-line treatment appears to be made primarily based on side effect profile in osteoarthritis guidelines. (Zhang, 2008) The most recent Cochrane review on this subject suggests that non-steroidal anti-inflammatory drugs (NSAIDs) are more efficacious for osteoarthritis than acetaminophen in terms of pain reduction, global assessments and improvement of functional status. No significant difference was found between overall safety, although patients taking NSAIDs were more likely to experience an adverse GI event. It is important to note that the median trial duration was only 6 weeks. (Towheed, 2008) See NSAIDs; NSAIDs, GI symptoms & cardiovascular risk; & NSAIDs, hypertension and renal function.

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*Low back pain (chronic):* Both acetaminophen and NSAIDs have been recommended as first-line therapy for low back pain. There is insufficient evidence to recommend one medication over the other. Selection should be made on a case-by-case basis based on weighing efficacy vs. side effect profile. In the past many low back pain guidelines recommended acetaminophen as a first-line treatment but recent systematic reviews either failed to find evidence to support the view that acetaminophen was effective for the treatment of non-specific low back pain (Davies, 2008) or found that there was only "fair" quality evidence to support use vs. "good" quality evidence for NSAIDs. (Chou, 2007) Problems with research in this area include a lack of large high quality trials, inadequate reporting of methods and results, and choice of treatment contrasts. Further research on this topic has been suggested. It appears that part of the reason that acetaminophen was recommended as a first-line treatment over NSAIDs in most guidelines, in part, was that acetaminophen appeared to have less adverse effects. (Roelofs-Cochrane, 2008) See adverse effects below.

*Adverse effects:* Hepatotoxicity: Acetaminophen overdose is a well-known cause of acute liver failure. Hepatotoxicity from therapeutic doses is unusual. (Hunt, 2007) A warning is given on all acetaminophen products that patients that consume  $\geq 3$  alcoholic drinks a day should discuss use with their physician, although a systematic review of acetaminophen use in alcoholic subjects concluded that there was little credible evidence to implicate therapeutic doses as a cause of fulminant hepatotoxicity in alcoholics. (Dart, 2007) Recent RCTs found that short-term treatment (3-5 days) of acetaminophen in newly abstinent alcoholic patients did not cause hepatic injury. (Kuffner, 2007) (Bartels, 2008) Acetaminophen, when used at recommended maximum doses, may induce ALT elevations  $>3 \times$  ULN in up to nearly 40% of subjects. Renal toxicity: Renal insufficiency occurs in 1 to 2% of patients with overdose. (Mazer, 2008) Hypertension and cardiovascular risk: Cohort analysis reveals that acetaminophen use is associated with hypertension but evidence from randomized controlled trials is limited. This risk is similar to that found for NSAIDs. (Forman, 2007) (Montgomery, 2008) An increased cardiovascular risk was found in the Nurse's Health Study. (Chan, 2006) (Laine, 2007) (Laine, 2008)

*Dose:* The recommended dose for mild to moderate pain is 650 to 1000 mg orally every 4 hours with a maximum of 4 g/day.

### **Actiq® (fentanyl lollipop)**

Not recommended for musculoskeletal pain. Actiq® (oral transmucosal fentanyl citrate), a fast-acting highly potent "lollipop" painkiller produced by Cephalon, is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Actiq is not for use in chronic pain; and it has a Black Box warning for abuse potential. See Opioids.

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## Acupuncture [DWC]

See Section 9792.24.1 of the California Code of Regulations, Title 8, under the Special Topics section. This section addresses the use of acupuncture for chronic pain in the workers' compensation system in California.

## Alendronate (Fosamax®)

See Bisphosphonates. Bisphosphonates are a class of drugs that inhibit osteoclast action and the resorption of bone. Alendronate (Fosamax®) is in this class.

## Alexander technique

See Education.

## Amitriptyline

Recommended. Amitriptyline is a tricyclic antidepressant. Tricyclics are generally considered a first-line agent unless they are ineffective, poorly tolerated, or contraindicated. See Antidepressants for chronic pain for general guidelines, as well as specific Tricyclics listing for more information and references.

## Anticonvulsants

See Anti-epilepsy drugs (AEDs)

## Antidepressants for chronic pain

Recommended as a first line option for neuropathic pain, and as a possibility for non-neuropathic pain. (Feuerstein, 1997) (Perrot, 2006) Tricyclics are generally considered a first-line agent unless they are ineffective, poorly tolerated, or contraindicated. Analgesia generally occurs within a few days to a week, whereas antidepressant effect takes longer to occur. (Saarto-Cochrane, 2005) Assessment of treatment efficacy should include not only pain outcomes, but also an evaluation of function, changes in use of other analgesic medication, sleep quality and duration, and psychological assessment. Side effects, including excessive sedation (especially that which would affect work performance) should be assessed. (Additional side effects are listed below for each specific drug.) It is recommended that these outcome measurements should be initiated at one week of treatment with a recommended trial of at least 4 weeks. The optimal duration of treatment is not known because most double-blind trials have been of short duration (6-12 weeks). It has been suggested that if pain is in remission for 3-6 months, a gradual tapering of anti-depressants may be undertaken. (Perrot, 2006) (Schnitzer, 2004) (Lin-JAMA, 2003) (Salerno, 2002) (Moulin, 2001) (Fishbain, 2000) (Taylor, 2004) (Gijnsman, 2004) (Jick-JAMA, 2004) (Barbui, 2004) (Asnis, 2004) (Stein, 2003) (Pollack, 2003) (Ticknor, 2004) (Staiger, 2003) Long-term effectiveness of anti-depressants has not been established. (Wong, 2007) The effect of this class of medication in combination with other classes of drugs has not been well researched. (Finnerup, 2005) The “number needed to treat” (NNT) methodology (calculated as

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

the reciprocal value of the response rate on active and placebo) has been used to calculate efficacy of the different classes of antidepressants. (Sindrup, 2005)

***Specifically studied underlying pain etiologies:*** (also see below for specific drugs)

***Neuropathic pain:*** Recommended (tricyclic antidepressants) as a first-line option, especially if pain is accompanied by insomnia, anxiety, or depression. (Saarto-Cochrane, 2007) (ICSI, 2007) Other recent reviews recommended both tricyclic antidepressants and SNRIs (i.e., duloxetine and venlafaxine) as first line options. (Dworkin, 2007) (Finnerup, 2007)

***Non-neuropathic pain:*** Recommended as an option in depressed patients, but effectiveness is limited. Non-neuropathic pain is generally treated with analgesics and anti-inflammatories. In guidelines for painful rheumatic conditions recommended by Perrot, it was suggested that antidepressants may be prescribed as analgesics in non-depressed patients, with the first-line choice being tricyclics initiated at a low dose, increasing to a maximally tolerated dose. (Perrot, 2006)

***Specific studied disease states***

***Fibromyalgia:*** There have been 25 controlled trials that have studied the use of antidepressants for fibromyalgia, including 3 meta-analyses. Except for good results found with duloxetine and fibromyalgia (Arnold, 2007), the results generally show limited effectiveness on only a minority of patients for this condition, and most of these studies evaluated tricyclics. (Perrot, 2006) (Moulin, 2001) A review of two double blind, placebo controlled trials concluded that duloxetine was safe and effective in women with fibromyalgia for up to 12 weeks (with long-term studies needed). (Arnold, 2007) There appears to be a large placebo effect of this class of medications in treatment of this condition. (Saarto-Cochrane, 2007) Another review indicated that there is strong evidence that amitriptyline is effective for fibromyalgia; more information is needed regarding the role of SNRIs and SSRIs, so tricyclics may also be used for the treatment of fibromyalgia. (Goldenberg, 2007)

***Low Back Pain: Chronic:*** A systematic review indicated that tricyclic antidepressants have demonstrated a small to moderate effect on chronic low back pain (short-term pain relief), but the effect on function is unclear. This effect appeared to be based on inhibition of norepinephrine reuptake. SSRIs have not been shown to be effective for low back pain (there was not a significant difference between SSRIs and placebo) and SNRIs have not been evaluated for this condition. (Chou, 2007) Reviews that have studied the treatment of low back pain with tricyclic antidepressants found them to be slightly more effective than placebo for the relief of pain. A non-statistically significant improvement was also noted in improvement of functioning. SSRIs do not appear to be beneficial. (Perrot, 2006)

***Radiculopathy:*** Antidepressants are an option, but there are no specific medications that have been proven in high quality studies to be efficacious for treatment of lumbosacral radiculopathy. (Dworkin, 2007)

***Osteoarthritis:*** No studies have specifically studied the use of antidepressants to treat pain from osteoarthritis. (Perrot, 2006) In depressed patients with osteoarthritis, improving depression symptoms was found to decrease pain and improve functional status. (Lin-JAMA, 2003)

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## **SPECIFIC ANTIDEPRESSANTS:**

**Tricyclic antidepressants** are recommended over selective serotonin reuptake inhibitors (SSRIs), unless adverse reactions are a problem. Caution is required because tricyclics have a low threshold for toxicity, and tricyclic antidepressant overdose is a significant cause of fatal drug poisoning due to their cardiovascular and neurological effects. Tricyclic antidepressants have been shown in both a meta-analysis (McQuay, 1996) and a systematic review (Collins, 2000) to be effective, and are considered a first-line treatment for neuropathic pain. (Namaka, 2004) (Dworkin, 2003) (Gilron, 2006) (Wolfe, 2004) (Dworkin, 2007) (Saarto-Cochrane, 2007) This class of medications works in both patients with normal mood and patients with depressed mood when used in treatment for neuropathic pain. (Sindrup, 2005) Indications in controlled trials have shown effectiveness in treating central post-stroke pain, post-herpetic neuralgia (Argoff, 2004), painful diabetic and non-diabetic polyneuropathy, and post-mastectomy pain. Negative results were found for spinal cord pain and phantom-limb pain, but this may have been due to study design. (Finnerup, 2005) Tricyclics have not demonstrated significance in randomized-control trials in treating HIV neuropathy, spinal cord injury, cisplatin neuropathy, neuropathic cancer pain, phantom limb pain or chronic lumbar root pain. (Dworkin, 2007) One review reported the NNT for at least moderate neuropathic pain relief with tricyclics is 3.6 (3-4.5), with the NNT for amitriptyline being 3.1 (2.5-4.2). The NNT for venlafaxine, calculated using 3 studies, was reported to be 3.1 (2.2-5.1). (Saarto-Cochrane, 2007) Another review reported that the NNT for 50% improvement in neuropathic pain was 2 to 3 for tricyclic antidepressants, 4 for venlafaxine, and 7 for SSRIs (Perrot, 2008).

**Side-effect profile:** Tricyclics are contraindicated in patients with cardiac conduction disturbances and/or decompensation (they can produce heart block and arrhythmias) as well as for those patients with epilepsy. For patients > 40 years old, a screening ECG is recommended prior to initiation of therapy. (Dworkin, 2007) (ICSI, 2007) They can create anticholinergic side effects of dry mouth, sweating, dizziness, orthostatic hypotension, fatigue, constipation, and urinary retention. (Finnerup, 2005) To minimize side effects, it is suggested that titration should be slow and based on the patient's response. (Namaka, 2004) An alternative choice may be a SNRI. (Finnerup, 2005) (Sindrup, 2005) (Dworkin, 2007)

### **Dosing Information:**

**Amitriptyline: Neuropathic pain:** The starting dose may be as low as 10-25 mg at night, with increases of 10-25 mg once or twice a week up to 100 mg/day. (ICSI, 2007) The lowest effective dose should be used (Dworkin, 2007). **Fibromyalgia:** One review recommended the following dosing regimen: Start with low doses, such as 5-10 mg 1-3 hours before bedtime. Dose may be increased by 5 mg at two-week intervals; final dose is dependent upon efficacy and patient tolerability to side effects. Doses that have been studied range from 25 to 50 mg at bedtime. (Goldenberg, 2007)

### **Selective serotonin and norepinephrine reuptake inhibitors (SNRIs):**

**Duloxetine (Cymbalta®):** FDA-approved for anxiety, depression, diabetic neuropathy, and fibromyalgia. Used off-label for neuropathic pain and radiculopathy. Duloxetine is recommended as a first-line option for diabetic neuropathy. (Dworkin, 2007) No high quality evidence is reported to support the use of duloxetine for lumbar radiculopathy. (Dworkin, 2007) More studies are needed to determine the efficacy of duloxetine for other types of neuropathic pain.

**Side effects:** CNS: dizziness, fatigue, somnolence, drowsiness, anxiety (3% vs.2% for placebo), insomnia (8-13% vs. 6-7% for placebo). GI: nausea and vomiting (5-30%), weight loss (2%).

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Duloxetine can worsen diabetic control in some patients. It also causes sexual dysfunction. (Maizels, 2005)

*Dosing:* 60 mg once a day as an off-label option for chronic pain syndromes. Dosage adjustment may be required in patients with renal insufficiency.

*Venlafaxine (Effexor®):* FDA-approved for anxiety, depression, panic disorder and social phobias. Off-label use for fibromyalgia, neuropathic pain, and diabetic neuropathy.

*Side-effect profile:* CNS: ( $\geq 5\%$ ) drowsiness, weakness, dizziness, dry mouth, insomnia, nervousness/anxiety (13/6% vs. 6/3%), tremor, headache, seizures. GI: N&V, constipation, weight loss (2-18%). Pre-existing hypertension should be controlled. Cholesterol may be increased (5%). Sexual dysfunction has also been noted. (Maizels, 2005) (ICSI, 2007)

*Dosing: Neuropathic pain (off-label indication):* 37.5 mg once daily, increase by 37.5 mg per week up to 300 mg daily. (Maizels, 2005) (ICSI, 2007) *Trial period:* Some relief may occur in first two weeks; full benefit may not occur until six weeks. Withdrawal effects can be severe. Abrupt discontinuation should be avoided and tapering is recommended before discontinuation.

***Bupropion (Wellbutrin®)***, a second-generation non-tricyclic antidepressant (a noradrenaline and dopamine reuptake inhibitor) has been shown to be effective in relieving neuropathic pain of different etiologies in a small trial (41 patients). (Finnerup, 2005) While bupropion has shown some efficacy in neuropathic pain there is no evidence of efficacy in patients with non-neuropathic chronic low back pain. (Katz, 2005) Furthermore, a recent review suggested that bupropion is generally a third-line medication for diabetic neuropathy and may be considered when patients have not had a response to a tricyclic or SNRI. (Dworkin, 2007)

*Side-effect profile:* Headache, agitation, insomnia, anorexia, weight loss

*Dosing Information: Neuropathic pain (off-label indication):* 100 mg once daily, increase by 100 mg per week up to 200 mg twice daily. (Maizels, 2005)

***Selective serotonin reuptake inhibitors (SSRIs)***, a class of antidepressants that inhibit serotonin reuptake without action on noradrenaline, are controversial based on controlled trials. (Finnerup, 2005) (Saarto-Cochrane, 2005) It has been suggested that the main role of SSRIs may be in addressing psychological symptoms associated with chronic pain. (Namaka, 2004) More information is needed regarding the role of SSRIs and pain.

### Antiepilepsy drugs (AEDs)

*Anti-epilepsy drugs (AEDs) are also referred to as anti-convulsants.*

Recommended for neuropathic pain (pain due to nerve damage). (Gilron, 2006) (Wolfe, 2004) (Washington, 2005) (ICSI, 2005) (Wiffen-Cochrane, 2005) (Attal, 2006) (Wiffen-Cochrane, 2007) (Gilron, 2007) (ICSI, 2007) (Finnerup, 2007) There is a lack of expert consensus on the treatment of neuropathic pain in general due to heterogeneous etiologies, symptoms, physical signs and mechanisms. Most randomized controlled trials (RCTs) for the use of this class of medication for neuropathic pain have been directed at postherpetic neuralgia and painful polyneuropathy (with diabetic polyneuropathy being the most common example). There are few RCTs directed at central pain and none for painful radiculopathy. (Attal, 2006) The choice of specific agents reviewed below will depend on the balance between effectiveness and adverse reactions. See also specific drug listings below: Gabapentin (Neurontin®); Pregabalin (Lyrica®);

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Lamotrigine (Lamictal®); Carbamazepine (Tegretol®); Oxcarbazepine (Trileptal®); Phenytoin (Dilantin®); Topiramate (Topamax®); Levetiracetam (Keppra®); Zonisamide (Zonegran®); & Tiagabine (Gabitril®)

*Outcome:* A “good” response to the use of AEDs has been defined as a 50% reduction in pain and a “moderate” response as a 30% reduction. It has been reported that a 30% reduction in pain is clinically important to patients and a lack of response of this magnitude may be the “trigger” for the following: (1) a switch to a different first-line agent (TCA, SNRI or AED are considered first-line treatment); or (2) combination therapy if treatment with a single drug agent fails. (Eisenberg, 2007) (Jensen, 2006) After initiation of treatment there should be documentation of pain relief and improvement in function as well as documentation of side effects incurred with use. The continued use of AEDs depends on improved outcomes versus tolerability of adverse effects. AEDs are associated with teratogenicity, so they must be used with caution in woman of childbearing age. Preconception counseling is recommended for anticonvulsants (due to reductions in the efficacy of birth control pills). (Clinical Pharmacology, 2008)

*Specifically studied disease states:* (also see below for specific drugs)

*Painful polyneuropathy:* AEDs are recommended on a trial basis (gabapentin/pregabalin) as a first-line therapy for painful polyneuropathy (with diabetic polyneuropathy being the most common example). The other first-line options are a tri-cyclic antidepressant (if tolerated by the patient), or a SNRI antidepressant (such as duloxetine). (Attal, 2006) (Jensen, 2006)

*Postherpetic neuralgia:* Gabapentin and pregabalin are recommended. (Attal, 2006) (Backonja, 2004)

*Central pain:* There are so few trials (with such small sample size) that treatment is generally based on that recommended for peripheral neuropathy, with gabapentin and pregabalin recommended. Lamotrigine has been found to be effective for central post-stroke pain (see below for specific drugs), and gabapentin has also been found to be effective. (Backonja, 2004)

*Chronic non-specific axial low back pain:* A recent review has indicated that there is insufficient evidence to recommend for or against antiepileptic drugs for axial low back pain. (Chou, 2007) There is one randomized controlled study that has investigated topiramate for chronic low back pain. (Muehlbacher, 2006) This study specifically stated that there were no other studies to evaluate the use of this medication for this condition. Patients in this study were excluded if they were taking opioids. No patient had undergone back surgery. In terms of the Oswestry low back pain questionnaire scale, the differences in the placebo group and treatment group were significant, although the mean score in both groups remained  $\geq 34$ . Reduction in pain rating index appeared to be correlated with weight reduction. See Topiramate below. The authors felt additional research was required to see if the results could be replicated and how long-lasting benefits were. There are no other articles available that evaluate the use of other anti-epilepsy drugs in the treatment of chronic non-specific, non-neuropathic axial low back pain.

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*Treatment of pain associated with osteoarthritis of the hip:* Not indicated

*Spinal cord injury:* Gabapentin is recommended for chronic neuropathic pain. (Levendoglu, 2004)

*CRPS:* Gabapentin has been recommended (Serpell, 2002)

*Fibromyalgia:* Gabapentin and pregabalin have been found to be safe and efficacious to treat pain and other symptoms. (Arnold, 2007) (Crofford, 2005) Pregabalin is FDA approved for fibromyalgia.

*Lumbar spinal stenosis:* Gabapentin produced statistically significant improvement in walking distance, decrease in pain with movement and sensory deficit in a pilot study. (Yaksi, 2007)

*Myofascial pain:* Not recommended. There is a lack of evidence to demonstrate that AEDs significantly reduce the level of myofascial or other sources of somatic pain. (Wiffen-Cochrane, 2005) (Washington, 2005)

*Postop pain:* AEDs may also be an option for postoperative pain, resulting in decreased opioid consumption. (Peng, 2007) (Buvanendran, 2007)

### **SPECIFIC ANTI-EPILEPSY DRUGS:**

***Gabapentin (Neurontin®), Gabarone™, generic available*** has been shown to be effective for treatment of diabetic painful neuropathy and postherpetic neuralgia and has been considered as a first-line treatment for neuropathic pain. (Backonja, 2002) (ICSI, 2007) (Knotkova, 2007) (Eisenberg, 2007) (Attal, 2006) This RCT concluded that gabapentin monotherapy appears to be efficacious for the treatment of pain and sleep interference associated with diabetic peripheral neuropathy and exhibits positive effects on mood and quality of life. (Backonja, 1998) It has been given FDA approval for treatment of post-herpetic neuralgia. The number needed to treat (NNT) for overall neuropathic pain is 4. It has a more favorable side-effect profile than Carbamazepine, with a number needed to harm of 2.5. (Wiffen2-Cochrane, 2005) (Zaremba, 2006) Gabapentin in combination with morphine has been studied for treatment of diabetic neuropathy and postherpetic neuralgia. When used in combination the maximum tolerated dosage of both drugs was lower than when each was used as a single agent and better analgesia occurred at lower doses of each. (Gilron-NEJM, 2005) Recommendations involving combination therapy require further study.

*Mechanism of action:* This medication appears to be effective in reducing abnormal hypersensitivity (allodynia and hyperalgesia), to have anti-anxiety effects, and may be beneficial as a sleep aid. (Arnold, 2007)

*Specific pain states:*

There is limited evidence to show that this medication is effective for postoperative pain, where there is fairly good evidence that the use of gabapentin and gabapentin-like compounds results in decreased opioid consumption. This beneficial effect, which may be related to an anti-anxiety effect, is accompanied by increased sedation and dizziness. (Peng, 2007) (Buvanendran, 2007) (Menigaux, 2005) (Pandey, 2005)

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*Spinal cord injury:* Recommended as a trial for chronic neuropathic pain that is associated with this condition. (Levendoglu, 2004)

*CRPS:* Recommended as a trial. (Serpell, 2002)

*Fibromyalgia:* Recommended as a trial. (Arnold, 2007)

*Lumbar spinal stenosis:* Recommended as a trial, with statistically significant improvement found in walking distance, pain with movement, and sensory deficit found in a pilot study. (Yaksi, 2007)

*Side-Effect Profile:* Gabapentin has a favorable side-effect profile, few clinically significant drug-drug interactions and is generally well tolerated; however, common side effects include dizziness, somnolence, confusion, ataxia, peripheral edema, and dry mouth. (Eisenberg, 2007) (Attal, 2006) Weight gain is also an adverse effect.

*Dosing Information:*

*Postherpetic neuralgia* – Starting regimen of 300 mg once daily on Day 1, then increase to 300 mg twice daily on Day 2; then increase to 300 mg three times daily on Day 3. Dosage may be increased as needed up to a total daily dosage of 1800 mg in three divided doses. Doses above 1800 mg/day have not demonstrated an additional benefit in clinical studies. (Neurontin package insert)

*Diabetic neuropathy (off-label indication)* – Gabapentin dosages range from 900 mg to 3600 mg in three divided doses (Backonja, 2002) (Eisenberg, 2007). Gabapentin is 100% renally excreted.

*Recommended Trial Period:* One recommendation for an adequate trial with gabapentin is three to eight weeks for titration, then one to two weeks at maximum tolerated dosage. (Dworkin, 2003) The patient should be asked at each visit as to whether there has been a change in pain or function. Current consensus based treatment algorithms for diabetic neuropathy suggest that if inadequate control of pain is found, a switch to another first-line drug is recommended. Combination therapy is only recommended if there is no change with first-line therapy, with the recommended change being at least 30%. (TCA, SNRI or AED). (Jensen, 2006) (Eisenberg, 2007)

*Weaning and/or changing to another drug in this class:* Gabapentin should not be abruptly discontinued, although this recommendation is made based on seizure therapy. Weaning and/or switching to another drug in this class should be done over the minimum of a week. (Neurontin package insert) *When to switch to pregabalin:* If there is evidence of inadequate response, intolerance, hypersensitivity or contraindications. There have been no head-to-head comparison trials of the two drugs.

***Pregabalin (Lyrica®)***, no generic available) has been documented to be effective in treatment of diabetic neuropathy and postherpetic neuralgia, has FDA approval for both indications, and is considered first-line treatment for both. This medication is designated as a Schedule V controlled substance because of its causal relationship with euphoria. (Blommel, 2007) This medication also has an anti-anxiety effect. Pregabalin is being considered by the FDA as treatment for generalized anxiety disorder and social anxiety disorder. In June 2007 the FDA announced the approval of pregabalin as the first approved treatment for fibromyalgia. (ICSI, 2007) (Tassone, 2007) (Knotkova, 2007) (Eisenberg, 2007) (Crofford, 2005) (Stacey, 2008) Dose adjustment is necessary in patients with renal insufficiency. The antiepileptic agents gabapentin and pregabalin have attained widespread usage in the treatment of painful diabetic peripheral neuropathy (DPN). This pooled analysis of 7 randomized controlled trials comparing

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different doses and frequencies of pregabalin for painful DPN concluded that pregabalin at doses of 150, 300, and 600 mg daily is associated with dose-related relief of pain and reduction in sleep interference in patients with painful DPN. (Freeman, 2008)

*Side-Effect Profile:* Pregabalin has been associated with many side effects including edema, CNS depression, weight gain, and blurred vision. Somnolence and dizziness have been reported to be the most common side effects related to tolerability. (Tassone, 2007) (Attal, 2006) It has been suggested that this drug be avoided if the patient has a problem with weight gain. (Jensen, 2006)

*Dosing Information:*

*Diabetic neuropathy* – Begin with 50 mg 3 times a day; may be increased in one week based on tolerability and effect to a maximum of 300 mg/day. (Doses up to 600 mg/day were evaluated with no additional benefit and increase in side effects.)

*Postherpetic neuralgia* - Begin with 50 mg three times a day for one week; may be increased to 100 mg three times a day after one week based on tolerability and effect. Dose may be increased as tolerated after two to four weeks up to 300 mg twice daily (maximum dose 600 mg/day). (ICSI, 2007)

*Trial period:* There is no established trial period, but the onset of action is thought to be less than 1 week. (Attal, 2006)

*Weaning:* Do not discontinue pregabalin abruptly and weaning should occur over a one-week period. Withdrawal effects have been reported after abrupt discontinuation.

**Lamotrigine (Lamictal®, generic available)** has been proven to be moderately effective for treatment of trigeminal neuralgia, HIV, and central post-stroke pain; (Backonja, 2002) (Namaka, 2004) (Maizels, 2005) (ICSI, 2005) (Dworkin, 2003) (Wiffen-Cochrane, 2007). It has not been shown to be effective for diabetic neuropathy. Due to side-effects and slow titration period, lamotrigine is not generally recommended as a first-line treatment for neuropathic pain. (Dworkin, 2003) (ICSI, 2007) Furthermore, a recent Cochrane review determined that although there is some evidence that lamotrigine may be effective for HIV neuropathy and post-stroke pain, this drug does not have a “significant place in therapy at present.” This was partly due to the availability of more effective treatments including other AEDs and antidepressants. (Wiffen-Cochrane, 2007)

*Side-Effect Profile:* Lamotrigine is associated with many side effects, including a life-threatening skin rash, Stevens-Johnson syndrome (incidence 1/1000), and it has been reported that up to 7% developed a skin rash that may be dose-dependent. (Wiffen-Cochrane, 2007) There is a black box warning regarding skin rashes for this medication. The drug should be discontinued at first sign of rash. (Eisenberg, 2007) While current guidelines recommend discontinuing lamotrigine in patients who develop rash, cases that develop benign rash can be rechallenged without adverse consequences, but very slow titration of lamotrigine is crucial to the reduction of rash recurrence rate. The recommended dosage schedule is: 5 mg every day or every second day for 14 days, increased by 5 mg every 14th day to 25 mg a day. (P-Codrea Tigarar, 2005) (Lorberg, 2008) Other side effects include dizziness, nausea, headache and fatigue.

*Dosing Information:*(off-label indication) Begin with 25 mg daily; then titrate up by 25 mg to 50 mg every 1-2 weeks up to 400 mg/day; titration must occur slowly and tapering should occur upon discontinuation. (ICSI, 2007)

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**Carbamazepine** (*Tegretol®*, *Tegretol®-XR*, *Carbatrol®*, *Epitol®*, *Equetro™*, *generic available*) has been shown to be effective for trigeminal neuralgia (Backonja, 2002) (ICSI, 2007) (Finnerup, 2005) and has been FDA approved for this indication. The NNT for this medication for trigeminal neuralgia has been reported as 2.6. (Backonja, 2002)

*Side Effect Profile:* Carbamazepine's use is often limited because of side-effects, (Knotkova, 2007) including ataxia, cognitive decreases (Namaka, 2004), dizziness, somnolence, CNS depression, hyponatremia, nausea and vomiting, skin rashes (rarely Stevens-Johnson Syndrome has been reported) and hematologic disorders, including agranulocytosis and aplastic anemia. There is a black box warning regarding development of potentially fatal blood cell abnormalities following the use of carbamazepine, and the drug should be discontinued at the first sign of a rash. Pretreatment CBC should be obtained for monitoring purposes; other monitoring parameters include: CBC with platelet count, reticulocytes, serum iron, lipid panel, liver function tests, urinalysis, BUN, serum carbamazepine levels, thyroid function tests, serum sodium; ophthalmic exams (pupillary reflexes). Patient should also be observed for excessive sedation during initial therapy or when increasing dose. Additionally, a long-term effect of weight gain has been reported. This medication also has significant drug-drug interactions. The number needed to treat (NNT) for this medication for overall neuropathic pain is 2.5; while the number needed to harm found in the Cochrane review was 3.7. (Wiffen-Cochrane, 2005)

*Dosing Information:*

*Trigeminal neuralgia* – Begin with 100 mg twice daily with food; increase in increments of 100 mg twice daily as needed as tolerated. Usual dose is between 400-800 mg daily in two divided doses. Maximum dose 1200 mg/day.

**Oxcarbazepine** (*Trileptal®*, *generic available*) has demonstrated benefits for treating neuropathic pain, specifically trigeminal neuralgia and diabetic neuropathy (ICSI, 2007).

*Side-Effect Profile:* Similar side-effect profile to carbamazepine (see above). Generally better tolerated when compared to carbamazepine and fewer drug-drug interactions (ICSI, 2007) Serum sodium should be monitored (i.e., especially during initial three-month period).

*Dosing Information:* *Trigeminal neuralgia* (off-label indication) - Titrate as tolerated to effect, using recommended dosage titration schedules. Starting doses of 150 mg to 300 mg twice daily; may be titrated by no more than 600 mg/day at weekly intervals to a maximum of 2400 mg daily. Most patients respond to doses between 900 mg—2400 mg/day. (ICSI, 2007) Dose adjustment is necessary in patients with renal insufficiency; use in patients with severe hepatic insufficiency has not been established.

### Other Antiepileptic Drugs

**Phenytoin** (*Dilantin®*, *Phenytek™*, *generic available*) has been shown to have limited effectiveness to treat neuropathic pain, except for possible use in acute flares above baseline, and then, given as an IV injection. (Namaka, 2004)

**Topiramate** (*Topamax®*, *no generic available*) has been shown to have variable efficacy, with failure to demonstrate efficacy in neuropathic pain of “central” etiology. It is still considered for use for neuropathic pain when other anticonvulsants fail. Topiramate has recently been investigated as an adjunct treatment for obesity, but the side effect profile limits its use in this regard. (Rosenstock, 2007)

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*Levetiracetam (Keppra®), Zonisamide (Zonegran®), and Tiagabine (Gabitril®)*, are among the antiepileptic drugs (AEDs) most recently approved, while these drugs may be effective for neuropathic pain, the ultimate role of these agents for pain requires further research and experience (ICSI, 2007) (Knotkova, 2007) (Eisenberg, 2007). In the interim, these agents should be used to treat neuropathic pain only when carbamazepine, gabapentin, or lamotrigine cannot be used. (Guay, 2003) In addition, underlying depression and anxiety symptoms may be exacerbated by levetiracetam. (Ettinger, 2007)

## **Anti-inflammatory medications**

For specific recommendations, see NSAIDs (non-steroidal anti-inflammatory drugs). Anti-inflammatories are the traditional first line of treatment, to reduce pain so activity and functional restoration can resume, but long-term use may not be warranted. (Van Tulder-Cochrane, 2000) A comprehensive review of clinical trials on the efficacy and safety of drugs for the treatment of low back pain concludes that available evidence supports the effectiveness of non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) in chronic LBP and of antidepressants in chronic LBP. (Schnitzer, 2004) See also Nonprescription Medications. COX-2 inhibitors (e.g., Celebrex) may be considered if the patient has a risk of GI complications, but not for the majority of patients. Generic NSAIDs and COX-2 inhibitors have similar efficacy and risks when used for less than 3 months, but a 10-to-1 difference in cost. (Rate of overall GI bleeding is 3% with COX-2's versus 4.5% with ibuprofen.) (Homik, 2003) For precautions in specific patient populations, see NSAIDs, GI symptoms & cardiovascular risk.

## **Antispasmodics**

See Muscle relaxants.

## **Antispasticity drugs**

See Muscle relaxants.

## **APAP**

APAP is an abbreviation for N-acetyl-para-aminophenol, which is acetaminophen. APAP is used especially when combined with a prescription drug. See Acetaminophen.

## **Aquatic therapy**

Recommended as an optional form of exercise therapy, where available, as an alternative to land-based physical therapy. Aquatic therapy (including swimming) can minimize the effects of gravity, so it is specifically recommended where reduced weight bearing is desirable, for example extreme obesity. For recommendations on the number of supervised visits, see Physical medicine. Water exercise improved some components of health-related quality of life, balance, and stair climbing in females with fibromyalgia, but regular exercise and higher intensities may be required to preserve most of these gains. (Tomas-Carus, 2007)

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## Autonomic test battery

Recommended. A standard autonomic protocol that compared side-to-side skin temperature, resting sweat output, and quantitative sudomotor axon reflex test (QSART) measurements are sensitive and reliable tools to formulate a correct diagnosis of CRPS I and can be combined to provide an improved set of diagnostic criteria for CRPS I. (Sandroni, 1998) (Wasner, 2002) Resting skin temperature (RST), resting sweat output (RSO), and quantitative sudomotor axon reflex test (QSART) are a recently developed test battery with some evidence to support its limited use in the diagnosis of CRPS-I. (Colorado, 2002)

## Avinza® (morphine sulfate)

Avinza capsules are a brand of modified-release morphine sulfate indicated for once daily administration for the relief of moderate to severe breakthrough pain requiring continuous, around-the-clock opioid therapy for an extended period of time, supplied by King Pharmaceuticals, Inc. See Opioids for recommendations and references.

## Baclofen

See CRPS, sympathetic and epidural blocks. See also Muscle relaxants.

## Barbiturate-containing analgesic agents (BCAs)

Not recommended for chronic pain. The potential for drug dependence is high and no evidence exists to show a clinically important enhancement of analgesic efficacy of BCAs due to the barbiturate constituents. (McLean, 2000) There is a risk of medication overuse as well as rebound headache. (Friedman, 1987). See also Opioids.

## Behavioral interventions

Recommended. The identification and reinforcement of coping skills is often more useful in the treatment of pain than ongoing medication or therapy, which could lead to psychological or physical dependence. See also Multi-disciplinary pain programs.

### **ODG Cognitive Behavioral Therapy (CBT) guidelines for chronic pain:**

Screen for patients with risk factors for delayed recovery, including fear avoidance beliefs. See Fear-avoidance beliefs questionnaire (FABQ).

Initial therapy for these “at risk” patients should be physical medicine for exercise instruction, using a cognitive motivational approach to physical medicine.

Consider separate psychotherapy CBT referral after 4 weeks if lack of progress from physical medicine alone:

- Initial trial of 3-4 psychotherapy visits over 2 weeks
- With evidence of objective functional improvement, total of up to 6-10 visits over 5-6 weeks (individual sessions)

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## **Benzodiazepines**

Not recommended for long-term use because long-term efficacy is unproven and there is a risk of dependence. Most guidelines limit use to 4 weeks. Their range of action includes sedative/hypnotic, anxiolytic, anticonvulsant, and muscle relaxant. Chronic benzodiazepines are the treatment of choice in very few conditions. Tolerance to hypnotic effects develops rapidly. Tolerance to anxiolytic effects occurs within months and long-term use may actually increase anxiety. A more appropriate treatment for anxiety disorder is an antidepressant. Tolerance to anticonvulsant and muscle relaxant effects occurs within weeks. (Baillargeon, 2003) (Ashton, 2005)

## **Bier's block**

Recommended as an option with bretylium for severe CRPS. Due to modest benefits and the invasiveness of the therapy, intravenous regional sympathetic block (Bier's block) with bretylium should be offered only after careful counseling, and should be followed by intensive physical therapy. For more information and references, see Regional sympathetic blocks; & CRPS, sympathetic and epidural blocks. Although there is very limited scientific evidence to support this treatment, it is recommended as an option in certain cases when there are no other alternatives. When the procedure is performed, it must be done in conjunction with a rehabilitation program. Any additional blocks must be based on objective evidence of improvement.

## **Biofeedback**

Not recommended as a stand-alone treatment, but recommended as an option in a cognitive behavioral therapy (CBT) program to facilitate exercise therapy and return to activity. There is fairly good evidence that biofeedback helps in back muscle strengthening, but evidence is insufficient to demonstrate the effectiveness of biofeedback for treatment of chronic pain. Biofeedback may be approved if it facilitates entry into a CBT treatment program, where there is strong evidence of success. As with yoga, since outcomes from biofeedback are very dependent on the highly motivated self-disciplined patient, we recommend approval only when requested by such a patient, but not adoption for use by any patient. EMG biofeedback may be used as part of a behavioral treatment program, with the assumption that the ability to reduce muscle tension will be improved through feedback of data regarding degree of muscle tension to the subject. The potential benefits of biofeedback include pain reduction because the patient may gain a feeling that he is in control and pain is a manageable symptom. Biofeedback techniques are likely to use surface EMG feedback so the patient learns to control the degree of muscle contraction. The available evidence does not clearly show whether biofeedback's effects exceed nonspecific placebo effects. It is also unclear whether biofeedback adds to the effectiveness of relaxation training alone. The application of biofeedback to patients with CRPS is not well researched. However, based on CRPS symptomology, temperature or skin conductance feedback modalities may be of particular interest. (Keefe, 1981) (Nouwen, 1983) (Bush, 1985) (Croce, 1986) (Stuckey, 1986) (Asfour, 1990) (Altmaier, 1992) (Flor, 1993) (Newton-John, 1995) (Spence, 1995) (Vlaeyen, 1995) (NIH-JAMA, 1996) (van Tulder, 1997) (Buckelew, 1998) (Hasenbring,

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

1999) (Dursun, 2001) (van Santen, 2002) (Astin, 2002) (State, 2002) (BlueCross BlueShield, 2004) This recent report on 11 chronic whiplash patients found that, after 4 weeks of myofeedback training, there was a trend for decreased disability in 36% of the patients. The authors recommended a randomized-controlled trial to further explore the effects of myofeedback training. (Voerman, 2006). See also Cognitive behavioral therapy (Psychological treatment).

### **ODG biofeedback therapy guidelines:**

Screen for patients with risk factors for delayed recovery, as well as motivation to comply with a treatment regimen that requires self-discipline. Initial therapy for these “at risk” patients should be physical medicine exercise instruction, using a cognitive motivational approach to PT.

Possibly consider biofeedback referral in conjunction with CBT after 4 weeks:

- Initial trial of 3-4 psychotherapy visits over 2 weeks
- With evidence of objective functional improvement, total of up to 6-10 visits over 5-6 weeks (individual sessions)
- Patients may continue biofeedback exercises at home

### **Biopsychosocial model of chronic pain**

See Chronic pain programs (functional restoration programs), which are recommended where there is access to programs with proven successful outcomes, for patients with conditions that put them at risk of delayed recovery, including the detailed "Criteria for use of multidisciplinary pain management programs" highlighted in blue. These treatment programs are based on the biopsychosocial model, one that views pain and disability in terms of the interaction between physiological, psychological and social factors.

### **Bisphosphonates**

Recommend treatment of bone resorption with bisphosphonate-type compounds as an option for patients with CRPS Type I. Not recommended for other chronic pain conditions. Significant improvement has been found in limited studies of intravenous clodronate and intravenous alendronate. Alendronate (Fosamax®) given in oral doses of 40 mg a day (over an 8 week period) produced improvements in pain, pressure tolerance and joint mobility. The effects may potentially involve avenues other than inhibition of bone resorption. (Manicourt, 2004) See also CRPS, medications. Bisphosphonates are a class of drugs that inhibit osteoclast action and the resorption of bone. Alendronate (Fosamax®) is in this class.

### **Boswellia Serrata Resin (Frankincense) [DWC]**

Boswellia Serrata Resin (Frankincense) is not recommended for chronic pain.

### **Botulinum toxin (Botox®; Myobloc®)**

Not generally recommended for chronic pain disorders, but recommended for cervical dystonia. See more details below.

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*Not recommended for the following: tension-type headache; migraine headache; fibromyositis; chronic neck pain; myofascial pain syndrome; & trigger point injections.*

Several recent studies have found no statistical support for the use of Botulinum toxin A (BTX-A) for any of the following:

- The evidence is mixed for migraine headaches. This RCT found that both botulinum toxin type A (BoNTA) and divalproex sodium (DVPX) significantly reduced disability associated with migraine, and BoNTA had a favorable tolerability profile compared with DVPX. (Blumenfeld, 2008) In this RCT of episodic migraine patients, low-dose injections of BoNTA into the frontal, temporal, and/or glabellar muscle regions were not more effective than placebo. (Saper, 2007) Botulinum neurotoxin is probably ineffective in episodic migraine and chronic tension-type headache (Level B). (Naumann, 2008)
- Myofascial analgesic pain relief as compared to saline. (Qerama, 2006)
- Use as a specific treatment for myofascial cervical pain as compared to saline. (Ojala, 2006) (Ferrante, 2005) (Wheeler, 1998)
- Injection in myofascial trigger points as compared to dry needling or local anesthetic injections. (Kamanli, 2005) (Graboski, 2005).

Recent systematic reviews have stated that current evidence does not support the use of BTX-A trigger point injections for myofascial pain. (Ho, 2006) Or for mechanical neck disease (as compared to saline). (Peloso-Cochrane, 2006) A recent study that has found statistical improvement with the use of BTX-A compared to saline. Study patients had at least 10 trigger points and no patient in the study was allowed to take an opioid in the 4 weeks prior to treatment. (Gobel, 2006)

*Recommended: cervical dystonia*, a condition that is not generally related to workers' compensation injuries (also known as spasmodic torticollis), and is characterized as a movement disorder of the nuchal muscles, characterized by tremor or by tonic posturing of the head in a rotated, twisted, or abnormally flexed or extended position or some combination of these positions. When treated with BTX-B, high antigenicity limits long-term efficacy. Botulinum toxin A injections provide more objective and subjective benefit than trihexyphenidyl or other anticholinergic drugs to patients with cervical dystonia.

*Recommended: chronic low back pain, if a favorable initial response predicts subsequent responsiveness, as an option in conjunction with a functional restoration program.* Some additional new data suggests that it may be effective for low back pain. (Jabbari, 2006) (Ney, 2006) Botulinum neurotoxin may be considered for low back pain (Level C). (Naumann, 2008)

### **Bretylium**

See Bier's block.

### **Buprenorphine**

Recommended for treatment of opiate addiction. Also recommended as an option for chronic pain, especially after detoxification in patients who have a history of opiate addiction (see below for specific recommendations). A schedule-III controlled substance, buprenorphine is a partial agonist at the mu-receptor (the classic morphine receptor) and an antagonist at the kappa-

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receptor (the receptor that is thought to produce alterations in the perception of pain, including emotional response). In recent years, buprenorphine has been introduced in most European countries as a transdermal formulation ("patch") for the treatment of chronic pain. Proposed advantages in terms of pain control include the following: (1) No analgesic ceiling; (2) A good safety profile (especially in regard to respiratory depression); (3) Decreased abuse potential; (4) Ability to suppress opioid withdrawal; & (5) An apparent antihyperalgesic effect (partially due to the effect at the kappa-receptor). (Kress, 2008) (Heit, 2008) (Johnson, 2005) (Landau, 2007)

**Available formulations:** *Buprenorphine hydrochloride: Buprenex®:* Supplied as an injection solution; *Subutex®:* Supplied as a sublingual tablet in 2 daily dosage strengths (2 mg or 8 mg). *Buprenorphine hydrochloride and naloxone hydrochloride: Suboxone®:* Also supplied as a sublingual tablet in 2 dosage strengths (2/0.5 mg or 8/2 mg). Developed to have a lower intravenous (IV) misuse potential. When injected IV, naloxone is intended to cause withdrawal effects in individuals who are opiate-dependent, and to prevent the "high-effect" related to opioids such as euphoria. *Pharmacokinetics:* After sublingual administration the onset of effect occurs in 30 to 60 minutes. Peak blood levels are found at 90 to 100 minutes, followed by a rapid decline until 6 hours, and then a gradual decline over more than 24 hours. (Helm, 2008) (Koppert, 2005)

### **Indications:**

*Treatment of opiate agonist dependence (FDA Approved indication includes sublingual Subutex® and Suboxone®):* Recommended. When used for treatment of opiate dependence, clinicians must be in compliance with the Drug Addiction Treatment Act of 2000. (SAMHSA, 2008) Buprenorphine's pharmacological and safety profile makes it an attractive treatment for patients addicted to opioids. Buprenorphine's usefulness stems from its unique pharmacological and safety profile, which encourages treatment adherence and reduces the possibilities for both abuse and overdose. Studies have shown that buprenorphine is more effective than placebo and is equally as effective as moderate doses of methadone in opioid maintenance therapy. Few studies have been reported on the efficacy of buprenorphine for completely withdrawing patients from opioids. In general, the results of studies of medically assisted withdrawal using opioids (e.g., methadone) have shown poor outcomes. Buprenorphine, however, is known to cause a milder withdrawal syndrome compared to methadone and for this reason may be the better choice if opioid withdrawal therapy is elected. (McNicholas, 2004) (Helm, 2008)

### **Bupropion (Wellbutrin®)**

Recommended as an option after other agents. While bupropion has shown some efficacy in neuropathic pain there is no evidence of efficacy in patients with non-neuropathic chronic low back pain. Furthermore, bupropion is generally a third-line medication for diabetic neuropathy and may be considered when patients have not had a response to a tricyclic or SNRI. See Antidepressants for chronic pain for general guidelines, as well as specific Bupropion listing for more information and references.

### **Calcitonin**

Recommended as a treatment option for patients with CRPS Type I with a contraindication for treatment of bone resorption with a bisphosphonate. Not recommended for other chronic pain conditions. Significant improvement has been found in limited studies of intravenous clodronate and intravenous alendronate. Alendronate (Fosamax®) given in oral doses of 40 mg a day (over

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an 8 week period) produced improvements in pain, pressure tolerance and joint mobility. (Manicourt, 2004) Mixed results have been found with intranasal calcitonin (Miacalcin®). (Sahin, 2005) (Appelboom, 2002) (Rowbathan, 2006) (Sharma, 2006) See also **CRPS**, medications. Calcitonin is a hormone known to participate in calcium and phosphorus metabolism.

### Cannabinoids

Not recommended. In total, 11 states have approved the use of medical marijuana for the treatment of chronic pain, but there are no quality controlled clinical data with cannabinoids. Restricted legal access to Schedule I drugs, such as marijuana, tends to hamper research in this area. It is also very hard to do controlled studies with a drug that is psychoactive because it is hard to blind these effects. At this time it is difficult to justify advising patients to smoke street-grade marijuana, presuming that they will experience benefit, when they may also be harmed. (Mackie, 2007) (Moskowitz, 2007) One of the first dose-response studies of cannabis in humans has found a window of efficacy within which healthy volunteers experienced relief from experimentally induced pain. But although mid-range doses provided some pain relief, high doses appeared to exacerbate pain. (Wallace, 2007) Results of a double-blind crossover study suggest that smoked cannabis may reduce pain intensity for patients with neuropathic pain, although the Food and Drug Administration (FDA), Substance Abuse and Mental Health Services Administration (SAMHSA), and the National Institute for Drug Abuse (NIDA) report that no sound scientific studies support the medicinal use of cannabis. Psychoactive effects were also seen, including feeling high, although these were less apparent at the lower dose. Of more concern, were effects on cognitive performance, which in this chronic pain population was at or below the threshold for impairment already at baseline. Cannabis use was associated with modest declines in cognitive performance, particularly learning and recall, especially at higher doses. The finding necessitates caution in the prescribing of medical marijuana for neuropathic pain, especially in instances in which learning and memory are integral to a patient's work and lifestyle. (Wilsey, 2008)

### Capsaicin, topical

Recommended only as an option in patients who have not responded or are intolerant to other treatments.

*Formulations:* Capsaicin is generally available as a 0.025% formulation (as a treatment for osteoarthritis) and a 0.075% formulation (primarily studied for post-herpetic neuralgia, diabetic neuropathy and post-mastectomy pain). There have been no studies of a 0.0375% formulation of capsaicin and there is no current indication that this increase over a 0.025% formulation would provide any further efficacy.

*Indications:* There are positive randomized studies with capsaicin cream in patients with osteoarthritis, fibromyalgia, and chronic non-specific back pain, but it should be considered experimental in very high doses. Although topical capsaicin has moderate to poor efficacy, it may be particularly useful (alone or in conjunction with other modalities) in patients whose pain has not been controlled successfully with conventional therapy. The number needed to treat in musculoskeletal conditions was 8.1. The number needed to treat for neuropathic conditions was

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5.7. (Robbins, 2000) (Keitel, 2001) (Mason-BMJ, 2004) The results from this RCT support the beneficial effects of 0.025% capsaicin cream as a first-line therapy for OA pain. (Altman, 1994) *Mechanism of action:* Capsaicin, which is derived from chili peppers, causes vasodilation, itching, and burning when applied to the skin. These actions are attributed to binding with nociceptors, which causes a period of enhanced sensitivity followed by a refractory period of reduced sensitivity. Topical capsaicin is superior to placebo in relieving chronic neuropathic and musculoskeletal pain. Capsaicin produces highly selective regional anesthesia by causing degeneration of capsaicin-sensitive nociceptive nerve endings, which can produce significant and long lasting increases in nociceptive thresholds. (Maroon, 2006)

*Adverse reactions:* Local adverse reactions were common (one out of three patients) but seldom serious (burning, stinging, erythema). Coughing has also been reported. See also CRPS, medications; Topical analgesics.

### **Carbamazepine (Tegretol®)**

See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Carbamazepine listing.

### **Carisoprodol (Soma®)**

Not recommended. This medication is not indicated for long-term use. Carisoprodol is a commonly prescribed, centrally acting skeletal muscle relaxant whose primary active metabolite is meprobamate (a schedule-IV controlled substance). Carisoprodol is now scheduled in several states but not on a federal level. It has been suggested that the main effect is due to generalized sedation and treatment of anxiety. Abuse has been noted for sedative and relaxant effects. In regular abusers the main concern is the accumulation of meprobamate. Carisoprodol abuse has also been noted in order to augment or alter effects of other drugs. This includes the following: (1) increasing sedation of benzodiazepines or alcohol; (2) use to prevent side effects of cocaine; (3) use with tramadol to produce relaxation and euphoria; (4) as a combination with hydrocodone, an effect that some abusers claim is similar to heroin (referred to as a “Las Vegas Cocktail”); & (5) as a combination with codeine (referred to as “Soma Coma”). (Reeves, 1999) (Reeves, 2001) (Reeves, 2008) (Schears, 2004) There was a 300% increase in numbers of emergency room episodes related to carisoprodol from 1994 to 2005. (DHSS, 2005) Intoxication appears to include subdued consciousness, decreased cognitive function, and abnormalities of the eyes, vestibular function, appearance, gait and motor function. Intoxication includes the effects of both carisoprodol and meprobamate, both of which act on different neurotransmitters. (Bramness, 2007) (Bramness, 2004) A withdrawal syndrome has been documented that consists of insomnia, vomiting, tremors, muscle twitching, anxiety, and ataxia when abrupt discontinuation of large doses occurs. This is similar to withdrawal from meprobamate. (Reeves, 2007) (Reeves, 2004) There is little research in terms of weaning of high dose carisoprodol and there is no standard treatment regimen for patients with known dependence. Most treatment includes treatment for symptomatic complaints of withdrawal. Another option is to switch to phenobarbital to prevent withdrawal with subsequent tapering. A maximum dose of phenobarbital is 500 mg/day and the taper is 30 mg/day with a slower taper in an outpatient setting. Tapering should be individualized for each patient. (Boothby, 2003) For more information and references, see Muscle relaxants. See also Weaning of medications.

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## **Catapres® (Clonidine)**

See Clonidine, intrathecal.

## **Celebrex®**

Celebrex® is the brandname for celecoxib, and it is produced by Pfizer. Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) that is a COX-2 selective inhibitor, a drug that directly targets COX-2, an enzyme responsible for inflammation and pain. See Anti-inflammatory medications. See NSAIDs (non-steroidal anti-inflammatory drugs) for specific patient decision-making criteria. Unlike other NSAIDs, celecoxib does not appear to interfere with the antiplatelet activity of aspirin and is bleeding neutral when patients are being considered for surgical intervention or interventional pain procedures.

## **Cesamet®**

See Nabilone.

## **Chiropractic treatment**

See Manual therapy & manipulation.

## **Chondroitin sulfate**

See Glucosamine (and Chondroitin Sulfate).

## **Chronic pain programs (functional restoration programs)**

Recommended where there is access to programs with proven successful outcomes, for patients with conditions that put them at risk of delayed recovery. Patients should also be motivated to improve and return to work, and meet the patient selection criteria outlined below. Also called Multidisciplinary pain programs or Interdisciplinary rehabilitation programs, these pain rehabilitation programs combine multiple treatments, and at the least, include psychological care along with physical therapy & occupational therapy (including an active exercise component as opposed to passive modalities). While recommended, the research remains ongoing as to (1) what is considered the “gold-standard” content for treatment; (2) the group of patients that benefit most from this treatment; (3) the ideal timing of when to initiate treatment; (4) the intensity necessary for effective treatment; and (5) cost-effectiveness. It has been suggested that interdisciplinary/multidisciplinary care models for treatment of chronic pain may be the most effective way to treat this condition. (Flor, 1992) (Gallagher, 1999) (Guzman, 2001) (Gross, 2005) (Sullivan, 2005) (Dysvik, 2005) (Airaksinen, 2006) (Schonstein, 2003) (Sanders, 2005) (Patrick, 2004) (Buchner, 2006) Unfortunately, being a claimant may be a predictor of poor long-term outcomes. (Robinson, 2004) These treatment modalities are based on the biopsychosocial model, one that views pain and disability in terms of the interaction between physiological, psychological and social factors. (Gatchel, 2005) There appears to be little

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scientific evidence for the effectiveness of multidisciplinary biopsychosocial rehabilitation compared with other rehabilitation facilities for neck and shoulder pain, as opposed to low back pain and generalized pain syndromes. (Karjalainen, 2003)

**Types of programs:** There is no one universal definition of what comprises interdisciplinary/multidisciplinary treatment. The most commonly referenced programs have been defined in the following general ways (Stanos, 2006):

(1) Multidisciplinary programs: Involves one or two specialists directing the services of a number of team members, with these specialists often having independent goals. These programs can be further subdivided into four levels of pain programs:

(a) Multidisciplinary pain centers (generally associated with academic centers and include research as part of their focus)

(b) Multidisciplinary pain clinics

(c) Pain clinics

(d) Modality-oriented clinics

(2) Interdisciplinary pain programs: Involves a team approach that is outcome focused and coordinated and offers goal-oriented interdisciplinary services. Communication on a minimum of a weekly basis is emphasized. The most intensive of these programs is referred to as a Functional Restoration Program, with a major emphasis on maximizing function versus minimizing pain. See Functional restoration programs.

**Types of treatment:** Components suggested for interdisciplinary care include the following services delivered in an integrated fashion: (a) physical treatment; (b) medical care and supervision; (c) psychological and behavioral care; (d) psychosocial care; (e) vocational rehabilitation and training; and (f) education.

**Predictors of success and failure:** As noted, one of the criticisms of interdisciplinary/multidisciplinary rehabilitation programs is the lack of an appropriate screening tool to help to determine who will most benefit from this treatment. Retrospective research has examined decreased rates of completion of functional restoration programs, and there is ongoing research to evaluate screening tools prior to entry. (Gatchel, 2006) The following variables have been found to be negative predictors of efficacy of treatment with the programs as well as negative predictors of completion of the programs: (1) a negative relationship with the employer/supervisor; (2) poor work adjustment and satisfaction; (3) a negative outlook about future employment; (4) high levels of psychosocial distress (higher pretreatment levels of depression, pain and disability); (5) involvement in financial disability disputes; (6) greater rates of smoking; (7) duration of pre-referral disability time; (8) prevalence of opioid use; and (9) pre-treatment levels of pain. (Linton, 2001) (Bendix, 1998) (McGeary, 2006) (McGeary, 2004) (Gatchel, 2005) Multidisciplinary treatment strategies are effective for patients with chronic low back pain (CLBP) in all stages of chronicity and should not only be given to those with lower grades of CLBP, according to the results of a prospective longitudinal clinical study reported in the December 15 issue of Spine. (Buchner, 2007) See also Chronic pain programs, early intervention; Chronic pain programs, intensity; Chronic pain programs, opioids; and Functional restoration programs.

### **Criteria for the general use of multidisciplinary pain management programs:**

Outpatient pain rehabilitation programs may be considered medically necessary when all of the following criteria are met:

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(1) An adequate and thorough evaluation has been made, including baseline functional testing so follow-up with the same test can note functional improvement; (2) Previous methods of treating chronic pain have been unsuccessful and there is an absence of other options likely to result in significant clinical improvement; (3) The patient has a significant loss of ability to function independently resulting from the chronic pain; (4) The patient is not a candidate where surgery or other treatments would clearly be warranted (if a goal of treatment is to prevent or avoid controversial or optional surgery, a trial of 10 visits may be implemented to assess whether surgery may be avoided); (5) The patient exhibits motivation to change, and is willing to forgo secondary gains, including disability payments to effect this change; & (6) Negative predictors of success above have been addressed.

Integrative summary reports that include treatment goals, progress assessment and stage of treatment, must be made available upon request and at least on a bi-weekly basis during the course of the treatment program. Treatment is not suggested for longer than 2 weeks without evidence of demonstrated efficacy as documented by subjective and objective gains. (Note: Patients may get worse before they get better. For example, objective gains may be moving joints that are stiff from lack of use, resulting in increased subjective pain.) However, it is also not suggested that a continuous course of treatment be interrupted at two weeks solely to document these gains, if there are preliminary indications that these gains are being made on a concurrent basis. Total treatment duration should generally not exceed 20 full-day sessions (or the equivalent in part-day sessions if required by part-time work, transportation, childcare, or comorbidities). (Sanders, 2005) Treatment duration in excess of 20 sessions requires a clear rationale for the specified extension and reasonable goals to be achieved. Longer durations require individualized care plans and proven outcomes, and should be based on chronicity of disability and other known risk factors for loss of function.

Inpatient pain rehabilitation programs: These programs typically consist of more intensive functional rehabilitation and medical care than their outpatient counterparts. They may be appropriate for patients who: (1) don't have the minimal functional capacity to participate effectively in an outpatient program; (2) have medical conditions that require more intensive oversight; (3) are receiving large amounts of medications necessitating medication weaning or detoxification; or (4) have complex medical or psychological diagnosis that benefit from more intensive observation and/or additional consultation during the rehabilitation process. (Keel, 1998) (Kool, 2005) (Buchner, 2006) (Kool, 2007) As with outpatient pain rehabilitation programs, the most effective programs combine intensive, daily biopsychosocial rehabilitation with a functional restoration approach. (BlueCross BlueShield, 2004) (Aetna, 2006) See Functional restoration programs.

### Chronic pain programs, early intervention

Recommended depending on identification of patients that may benefit from early intervention via a multidisciplinary approach, as indicated below. The likelihood of return to work diminishes significantly after approximately 3 months of sick leave. It is now being suggested that there is a place for interdisciplinary programs at a stage in treatment prior to the development of permanent disability, and this may be at a period of no later than 3 to 6 months after a disabling injury. (Robinson, 2004) (Gatchel, 2003) This early intervention has been referred to as "secondary treatment," and differs from the more traditional, palliative care pain programs by

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not only the earlier onset of treatment, but by treatment intensity and level of medical supervision. (Mayer 2003) Multidisciplinary treatment strategies are effective for patients with chronic low back pain (CLBP) in all stages of chronicity and should not only be given to those with lower grades of CLBP, according to the results of a prospective longitudinal clinical study reported in the December 15 issue of Spine. (Buchner, 2007) This study to evaluate RTW outcomes following proactive, combined clinical, occupational and case management-based interdisciplinary early intervention, provided in a workers' compensation environment at 4-10 weeks of onset of back pain, concluded that multimodal early intervention was more effective for workers with sub-acute back pain who are at high risk of occupational disability. (Schultz, 2008) Recommendations for identification of patients that may benefit from early intervention via a multidisciplinary approach:

- (a) The patient's response to treatment falls outside of the established norms for their specific diagnosis without a physical explanation to explain symptom severity.
- (b) The patient exhibits excessive pain behavior and/or complaints compared to that expected from the diagnosis.
- (c) There is a previous medical history of delayed recovery.
- (d) The patient is not a candidate where surgery or other treatments would clearly be warranted.
- (e) Inadequate employer support.
- (f) Loss of employment for greater than 4 weeks. The most discernable indication of at risk status is lost time from work of 4 to 6 weeks. (Mayer 2003) For general information see Chronic pain programs.

### Chronic pain programs, intensity

Recommend adjustment according to patient variables, as indicated below. Research is ongoing as to what treatments are most necessary as part of interdisciplinary treatment for patients with subacute and chronic pain, and how intense such delivery of care should be. The more traditional models of interdisciplinary pain management often provide what has been referred to as tertiary care; a more intensive, and often, more palliative treatment for chronic pain. Research as to the intensity of treatment that is required for earlier intervention remains ongoing ("secondary intervention" see Chronic pain programs, early intervention). Several examples show the difference in results based on intensity of treatment that occur based, in part, on variables such as gender, age, prognosis, diagnosis, and duration of pain. A recent study showed that for men with low back pain that had been "sick-listed" for an average of 3 months, there was no difference between extensive multidisciplinary treatment and usual care in terms of return to work. Significantly better results were found for men who received a "light treatment program" compared to usual care, and these results remained significant at 12, 18 and 24 months. (Skouen, 2002) On the other hand, an extensive program has been shown to be the most effective treatment modality for patients considered to be in categories of poor health, and poor prognosis who were "sick-listed" for the same period, although the effect tapers after one to two years. (Haldorsen, 2002) For general information see Chronic pain programs.

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## Chronic pain programs, opioids

Recommend assessing the effects of interdisciplinary pain programs on patients who remain on opioids throughout treatment, and to determine whether opioid use should be a screening factor for admission to or continuation in a program. The limited research that is available indicates that daily opioid use, in low doses, does not decrease effectiveness of chronic pain programs. Early research also indicates that simultaneous dependency/addiction programs with pain programs may be a viable option. Limited studies allow for an evaluation of the role of the chronic use of opioids on treatment success in interdisciplinary pain programs:

(1) The original Mayer et al. studies (Mayer, 1985) (Mayer, 1987): The comparison group was comprised of patients who were denied treatment by their insurers. A third group were those patients who were non-completers (10%). Prior to the actual functional restoration program (FRP), the patients in the program were treated with an introductory 3-6 week session that included tapering of habituating medications. The results of this pre-treatment may be reflected in the fact that only 15% of the treatment group were taking opioids versus 48% in the non-treatment comparison group (significant at  $P < 0.05$ ). The final results showed that 87% of the treatment group was actively working after two years compared to 41% of the non-treatment group (with results based on patients that the researchers were able to contact after the time period). Only 13% of the group of patients who decided not to complete the program (the third group) returned to work at one year. The role of the program design that included tapering of medications on treatment results was not discussed.

(2) Simultaneous opioid withdrawal and pain rehabilitation: Research evaluating simultaneous opioid withdrawal with pain rehabilitation programs (in an analysis of predominately female, non-workers' compensation patients), found that all patients that completed the program (regardless of opioid use on initial entry) showed decreased pain severity and catastrophizing, although those taking opioids had significantly higher scores at the three-week discharge for these variables. (Rome, 2004)

(3) Programs that don't emphasize opioid tapering: A more recent study of patient's receiving workers' compensation benefits in a program that did not stress opioid withdrawal found that at 6 months, 72.1% of opioid users returned to work versus 75.8% of non-opioid users, a non-significant difference. The mean dose of daily morphine equivalents was 28.63 mg (range 0.53 mg to 150 mg), which may limit the generalizability of the study. (Maclaren, 2006)

For general information see Chronic pain programs.

## Clonidine, Intrathecal

Recommended only after a short-term trial indicates pain relief in patients refractory to opioid monotherapy or opioids with local anesthetic. There is little evidence that this medication provides long-term pain relief (when used in combination with opioids approximately 80% of patients had < 24 months of pain relief) and no studies have investigated the neuromuscular, vascular or cardiovascular physiologic changes that can occur over long period of administration. Side effects include hypotension, and the medication should not be stopped abruptly due to the risk of rebound hypertension. The medication is FDA approved with an orphan drug intrathecal indication for cancer pain only. Clonidine is thought to act synergistically with opioids. Most studies on the use of this drug intrathecally for chronic non-malignant pain are limited to case reports. (Ackerman, 2003) Clonidine (Catapres) is a direct-acting adrenergic agonist prescribed

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historically as an antihypertensive agent, but it has found new uses, including treatment of some types of neuropathic pain.

*Additional studies:* One intermediate quality randomized controlled trial found that intrathecal clonidine alone worked no better than placebo. It also found that clonidine with morphine worked better than placebo or morphine or clonidine alone. (Ackermann, 2003) (Hassenbusch2, 2002) (Martin, 2001) (Raphael, 2002) (Roberts, 2001) (Siddall, 2000) (Taricco, 2006)

## **Cod liver oil [DWC]**

Cod liver oil is not recommended for chronic pain.

## **Codeine**

Recommended as an option for mild to moderate pain, as indicated below. Codeine is a schedule C-II controlled substance. It is similar to morphine. 60 mg of codeine is similar in potency to 600 mg of acetaminophen. It is widely used as a cough suppressant. It is used as a single agent or in combination with acetaminophen (Tylenol® with Codeine) and other products for treatment of mild to moderate pain.

*Adverse effects:* Common effects include CNS depression and hypotension. Drowsiness and constipation occur in > 10% of cases. Codeine should be used with caution in patients with a history of drug abuse. Tolerance as well as psychological and physical dependence may occur. Abrupt discontinuation after prolonged use may result in withdrawal. (AHFS Drug Information, 2008) (Clinical Pharmacology, 2008) (Lexi-Comp, 2008)

## **Cognitive behavioral therapy**

See Psychological treatment. See also Multi-disciplinary pain programs.

## **Cold lasers**

See Low level laser therapy (LLLT).

## **Complex Regional Pain Syndrome (CRPS)**

### **CRPS, diagnostic criteria**

Recommend using a combination of criteria as indicated below. There are no objective gold-standard diagnostic criteria for CRPS I or II. A comparison between three sets of diagnostic criteria for CRPS I concluded that there was a substantial lack of agreement between different diagnostic sets. (Perez, 2007)

#### **A. CRPS-I (RSD):**

The IASP (International Association for the Study of Pain) has defined this diagnosis as a variety of painful conditions following injury which appear regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event and often resulting in significant impairment of motor function, and showing variable progression over time. (Stanton-Hicks, 1995)

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Diagnostic criteria defined by IASP in 1995 were the following: (1) The presence of an initiating noxious event or cause of immobilization that leads to development of the syndrome; (2) Continuing pain, allodynia, or hyperalgesia which is disproportionate to the inciting event and/or spontaneous pain in the absence of external stimuli; (3) Evidence *at some time* of edema, changes in skin blood flow, or abnormal sudomotor activity in the pain region; & (4) The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain or dysfunction. Criteria 2-4 must be satisfied to make the diagnosis. These criteria were found to be able to pick up a true positive with few false negatives (sensitivity 99% to 100%), but their use resulted in a large number of false positives (specificity range of 36% to 55%). (Bruehl, 1999) (Galer, 1998) Up to 37% of patients with painful diabetic neuropathy may meet the clinical criteria for CRPS using the original diagnostic criteria. (Quisel, 2005) To improve specificity the IASP suggested the following criteria: (1) Continuing pain disproportionate to the inciting event; (2) A report of one *symptom* from each of the following four categories and one *physical finding* from two of the following four categories: (a) Sensory: hyperesthesia, (b) Vasomotor: temperature asymmetry or skin color changes or asymmetry, (c) Sudomotor/edema: edema or sweating changes or sweating asymmetry, or (d) Motor/trophic: reports of decreased range of motion or motor dysfunction (weakness/tremor or dystonia) or trophic changes: hair, nail, skin. This decreased the number of false positives (specificity 94%) but also decreased the number of true positives (sensitivity of 70%). (Bruehl, 1999)

The Harden Criteria have updated these with the following four criteria: (1) Continuing pain, which is disproportionate to any inciting event; & (2) Must report at least one symptom in three of the four following categories: (a) Sensory: Reports of hyperesthesia and/or allodynia; (b) Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry; (c) Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry; (d) Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin); & (3) Must display at least one sign at time of evaluation in two or more of the following categories: (a) Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement); (b) Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry; (c) Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry; (d) Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin); & 4. There is no other diagnosis that better explains the signs and symptoms (Harden, 2007)

The Washington State Department of Labor and Industries guidelines include the presence of four of the following physical findings: (1) Vasomotor changes: temperature/color change; (2) Edema; (3) Trophic changes: skin, hair, and/or nail growth abnormalities; (4) Impaired motor function (tremor, abnormal limb positioning and/or diffuse weakness that can't be explained by neuralgic loss or musculoskeletal dysfunction); (5) Hyperpathia/allodynia; or (6) Sudomotor changes: sweating. Diagnostic tests (only needed if four physical findings were not present): 3-phase bone scan that is abnormal in pattern characteristics for CRPS. (Washington, 2002)

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The State of Colorado Division of Workers' Compensation Medical Treatment Guidelines adopted the following diagnostic criteria in 2006: (1) The patient complains of pain (usually diffuse burning or aching); (2) Physical findings of at least vasomotor and/or sudomotor signs, allodynia and/or trophic findings add strength to the diagnosis; (3) At least two diagnostic testing procedures are positive and these procedures include the following: (a) Diagnostic imaging: Plain film radiography/triple phase bone scan, (b) Injections: Diagnostic sympathetic blocks, (c) Thermography: Cold water stress test/warm water stress test, or (d) Autonomic Test Battery. The authors provide the following caveat: Even the most sensitive tests can have false negatives, and the patient can still have CRPS-I, if clinical signs are strongly present. In patients with continued signs and symptoms of CRPS-I, further diagnostic testing may be appropriate. (Colorado, 2006)

Other authors have questioned the usefulness of diagnostic testing over and above history and physical findings. (Quisel, 2005) (Yung, 2003) (Perez2, 2005) A negative diagnostic test should not question a clinically typical presentation of CRPS and should not delay treatment. (Birklein, 2005)

### **B. CRPS-II (causalgia):**

Nerve damage can be detected by EMG but pain is not contained to that distribution. (Stanton-Hicks, 1995) CRPS I and II appear to be clinically similar. (Bruehl, 1999) CRPS-II is defined by the IASP as: (1) The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve; (2) Evidence at some time of edema, changes in skin blood flow, and/or abnormal sudomotor activity in the region of pain; & (3) The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction. The state of Colorado also uses the above criteria but adds that there must be documentation of peripheral nerve injury with pain initially in the distribution of the injured nerve. (Colorado, 2006)

### **C. Differential Diagnoses of CRPS**

These need to include local pathology, peripheral neuropathies, infectious processes, inflammatory and vascular disorders. (Quisel2, 2005) (Stanton-Hicks, 2006) Also include the following conditions: pain dysfunction syndrome; cumulative trauma syndrome; repetitive strain syndrome; overuse syndrome; tennis elbow; shoulder-hand syndrome; nonspecific thoracic outlet syndrome; fibromyalgia; posttraumatic vasoconstriction; undetected fracture; post-herpetic neuralgia; diabetic neuropathy. (Stanton-Hicks, 2004) See also Treatment for CRPS; Sympathetically maintained pain (SMP); CRPS, medications; CRPS, prevention; CRPS, sympathetic and epidural blocks.

### **CRPS, medications**

Recommended only as indicated below. Most medications have limited effectiveness. (Ribbers, 2003) (Quisel2, 2005)

1. Regional inflammatory reaction: Commonly used drugs are NSAIDs, corticosteroids and free-radical scavengers. There is some evidence of efficacy for topical DMSO cream, IV bisphosphonates and limited courses of oral corticosteroids. Corticosteroids are most effective when positive response is obtained with sympathetic blocks. NSAIDs are recommended but no trials have shown effectiveness in CRPS-I, and they are

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recommended primarily in early or very late stages. (Stanton-Hicks, 2004) (Sharma, 2006)

2. Stimulus-independent pain: The use of antidepressants, anticonvulsants, and opioids has been primarily extrapolated based on use for other neuropathic pain disorders. (See Antidepressants for chronic pain; Anticonvulsants for chronic pain; & Opioids for neuropathic pain.) Mexiletine, lidocaine patches and capsaicin are used but efficacy is not convincing. For central inhibition opiates, gabapentin, TCAs, GABA-enhancing drugs, and clonidine may be useful.

3. Stimulus-evoked pain: treatment is aimed at central sensitization. With NMDA receptor antagonists (ketamine and amantadine) convincing controlled trials are lacking, and these drugs are known for their side effects.

4. Sympathetically maintained pain (SMP):  $\alpha$ 1 adrenoceptor blocking agents (terazosin, prazosin, and phenoxybenzamine) have been shown to be effective in a case report. (Ghostine, 1984) Sympathetic suppressors such as guanethadine, reserpine, droperidol, or atropine (in general or IV block) have shown low effectiveness. (Perez, 2001) (Quisel2, 2005) Phentolamine (IV) has been used as an alternative to determine responsiveness to  $\alpha$ 1 adrenoceptor blocking agents. See also Sympathetically maintained pain (SMP).

5. Treatment of bone resorption with bisphosphonate-type compounds and calcitonin. Significant improvement has been found in limited studies of intravenous clodronate and intravenous alendronate. Adendronate (Fosamax®) given in oral doses of 40 mg a day (over an 8 week period) produced improvements in pain, pressure tolerance and joint mobility. (Manicourt DH, 2004) Mixed results have been found with intranasal calcitonin (Miacalcin®). (Sahin, 2005) (Appelboom, 2002) (Rowbathan, 2006) (Sharma, 2006)

### CRPS, prevention

Recommended as indicated below. Some cases of CRPS-I may be preventable. Post-stroke upper extremity hemiplegia (also known as shoulder-hand syndrome) may be prevented by early inpatient rehabilitation and avoidance of shoulder trauma to the affected arm. Post-fracture CRPS-I may be prevented with 500 mg vitamin C daily started upon diagnosis of fracture and continued through healing. (Quisel2, 2005)

### CRPS, spinal cord stimulators (SCS)

Recommended as indicated below. Spinal cord stimulators (SCS) should be offered only after careful counseling and patient identification and should be used in conjunction with comprehensive multidisciplinary medical management. SCS use has been associated with pain reduction in studies of patients with CRPS. (Kemler, 2000) (Kemler, 2004) (Kemler, 2008) CRPS patients implanted with SCS reported pain relief of at least 50% over a median follow-up period of 33 months. (Taylor, 2006) Moreover, there is evidence to demonstrate that SCS is a cost-effective treatment for CRPS-I over the long term. (Stanton-Hicks, 2006) (Mailis-Gagnon-Cochrane, 2004) (Kemler, 2000) Permanent pain relief in CRPS-I can be attained under long-term SCS therapy combined with physical therapy. (Harke, 2005) See Spinal cord stimulators (SCS).

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## CRPS, sympathectomy

Not recommended. The practice of surgical and chemical sympathectomy is based on poor quality evidence, uncontrolled studies and personal experience. Furthermore, complications of the procedure may be significant, in terms of both worsening the pain or producing a new pain syndrome; and abnormal forms of sweating (compensatory hyperhidrosis and pathological gustatory sweating). Therefore, more clinical trials of sympathectomy are required to establish the overall effectiveness and potential risks of this procedure. (Furlan, 2000) (Mailis-Cochrane, 2003) Sympathectomy is destruction of part of the sympathetic nervous system, and it is not generally accepted or widely used. Long-term success with this pain relief treatment is poor. Indications: Single extremity CRPS-I or SMP; distal pain only (should not be done if the proximal extremity is involved). Local anesthetic Stellate Ganglion Block or Lumbar Sympathetic Block consistently gives 90 to 100 percent relief each time a technically good block is performed (with measured rise in temperature). The procedure may be considered for individuals who have limited duration of relief from blocks. Permanent neurological complications are common. (State, 2002)

## CRPS, sympathetic and epidural blocks

Recommended only as indicated below, for a limited role, primarily for diagnosis of sympathetically mediated pain and as an adjunct to facilitate physical therapy. Detailed information about stellate ganglion blocks, thoracic sympathetic blocks, and lumbar sympathetic blocks is found in Regional sympathetic blocks. Recommendations for the use of sympathetic blocks are listed below. They are recommended for a limited role, primarily for diagnosis of sympathetically mediated pain and as an adjunct to facilitate physical therapy. It should be noted that sympathetic blocks are not specific for CRPS. See Sympathetically maintained pain (SMP). Repeated blocks are only recommended if continued improvement is observed. Systematic reviews reveal a paucity of published evidence supporting the use of local anesthetic sympathetic blocks for the treatment of CRPS and usefulness remains controversial. Less than 1/3 of patients with CRPS are likely to respond to sympathetic blockade. No controlled trials have shown any significant benefit from sympathetic blockade. (Varrassi, 2006) (Cepeda, 2005) (Hartrick, 2004) (Grabow, 2005) (Cepeda, 2002) (Forouzanfar, 2002) (Sharma, 2006) *Predictors of poor response*: Long duration of symptoms prior to intervention; Elevated anxiety levels; Poor coping skills; Litigation. (Hartrick, 2004) (Nelson, 2006) *Alternatives to regional sympathetic blocks*: may be necessary when there is evidence of coagulopathy, systemic infection, and/or post-surgical changes. These include peripheral nerve and plexus blocks and epidural administration of local anesthetics. *Mixed conduction blocks (central neural blocks)*: suggested when analgesia is insufficient by pharmacologic means to support physical therapy: (1) Implanted catheters at the brachial or lumbosacral plexus: allows for 1 to 2 weeks of therapy. Side effects include technical failure and infection; & (2) Epidural tunneled catheters: allows for long-term therapy: Side effects: same as above.

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

*Clonidine* has also been effective epidurally. (Stanton-Hicks, 2006) *Baclofen* has been demonstrated to be effective intrathecally to reduce dystonia. (van Hilten, 2000) *IV regional sympathetic blocks*: controversial due to varying success. Guanethidine was used, but is no longer available in the US. Bretylium and reserpine require daily blocks, and have potential side effects of transient syncope with apnea, orthostatic hypotension, pain with administration, nausea and vomiting. Bretylium provided more than 30% pain relief for a mean of 20 days compared to placebo. (Hord, 1992) Due to modest benefits and the invasiveness of the therapies, epidural clonidine injection and intravenous regional sympathetic block with bretylium should be offered only after careful counseling, and they should be followed by intensive physical therapy. Intravenous regional sympathetic block (Bier's block, 25 sessions) with guanethidine and lidocaine resulted in excellent pain relief and full restoration of both function and range of movement of the affected extremity in patients suffering from CRPS-I of the hand. (Paraskevas, 2005) Local or systemic parecoxib combined with lidocaine/clonidine IV regional analgesia is an effective treatment for CRPS-I in a dominant upper limb. (Frade, 2005) See also Sympathetically maintained pain (SMP); & Regional sympathetic blocks.

### CRPS, treatment

Recommended hierarchy of options as indicated below. The goal is to improve function. Multiple pathophysiological mechanisms are responsible including neuropathic (sympathetic and independently-maintained pain), and immunologic (regional inflammation and altered human leukocyte antigens). Both peripheral sensitization and central sensitization have been proposed. (Ribbers, 2003) (Stanton-Hicks, 2006) There are no evidence-based treatment guidelines but several groups have begun to organize treatment algorithms. Recommendations:

1. Rehabilitation: (a) Early stages: Build a therapeutic alliance. Analgesia, encouragement and education are key. Physical modalities include desensitization, isometric exercises, resisted range of motion, and stress loading. If not applied appropriately, PT can actually be detrimental. (b) Next steps: Increase flexibility with introduction of gentle active ROM and stretching (to treat accompanying myofascial pain syndrome). Other modalities may include muscle relaxants, trigger point injections and electrical stimulation (based on anecdotal evidence). Edema control may also be required (elevation, retrograde sympathetic blocks, diuretics and adrenoceptor blockers when sympathetically maintained pain-SMP is present). (c) Continued steps: Continue active ROM; stress loading; scrubbing techniques; isotonic strengthening; general aerobic conditioning; and postural normalization. (d) Final steps: Normalization of use; assessment of ergonomics, posture and modifications at home and work. In some cases increased requirements of analgesic medications, psychotherapy, invasive anesthetic techniques and SCS may be required. See CRPS, spinal cord stimulators.
2. Psychological treatment: Focused on improved quality of life, development of pain coping skills, cognitive-behavioral therapy, and improving facilitation of other modalities. (a) Early stages: education. (b) Next steps: clinical psychological assessment

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

(after 6 to 8 weeks): identification of stressors; identification of comorbid Axis I psychiatric disorders (depression, anxiety, panic and post-traumatic stress).

3. Pain management: (a) *Pharmacological*: antidepressants (particularly amitriptyline); anticonvulsants (particularly gabapentin); steroids; NSAIDs; opioids; calcitonin; bisphosphonates;  $\alpha$ 1 adrenoceptor antagonists (terazosin or phenoxybenzamine). The latter class of drugs has been helpful in SMP. Clonidine has been given transdermally and epidurally. (See CRPS, medications.) Bisphosphonates have some literature support in the presence of osteopenia. (Rho, 2002) (b) *Minimally invasive*: depends on degree of SMP, stage of rehabilitation (passive or active movement), and response to blocks. (See CRPS, sympathetic blocks.) Responders to sympathetic blocks (3 to 6 blocks with concomitant PT) may be all that is required. For non-responders somatic block or epidural infusion may be required to optimize analgesia for PT. (c) *More invasive*: After failure of progression or partial relief, consider tunneled epidural catheters for prolonged sympathetic or somatic blocks or neurostimulation with SCS in CRPS-I and II. See CRPS, spinal cord stimulators. Also consider peripheral nerve stimulation in CRPS-II and intrathecal drug delivery in patients with dystonia, failed neurostimulation, long-standing disease, multi-limb involvement and requirement of palliative care. (d) *Surgical*: Sympathectomy is not generally recommended, but has been considered in patients that respond to sympathetic blocks. Pre-procedure the patient should have outcomes assessed with radiofrequency and neurolytic procedures. (See CRPS, sympathectomy.) Motor Cortex Stimulation has been considered.

Outcome measures for all treatments of CRPS: Objective measures such as the Beck Depression Inventory, the State Trait Anxiety Inventory, McGill Pain Questionnaire-Short Form, the Pain Disability Index & the Treatment Outcomes in Pain Survey (the last three may not meet the APA standards for standardized test in clinical use). See Psychological evaluations. See also CRPS, diagnostic criteria; CRPS, medications; CRPS, prevention; CRPS, sympathetic blocks; & Sympathetically maintained pain (SMP). See also Spinal cord stimulators (SCS).

### CRPS

See Complex Regional Pain Syndrome (CRPS).

### Curcumin (tumeric) [DWC]

Curcumin (tumeric) is not recommended for the treatment of chronic pain.

### Cyclobenzaprine (Flexeril®)

Recommended as an option, using a short course of therapy. See Medications for chronic pain for other preferred options. Cyclobenzaprine (Flexeril®) is more effective than placebo in the management of back pain; the effect is modest and comes at the price of greater adverse effects. The effect is greatest in the first 4 days of treatment, suggesting that shorter courses may be better. (Browning, 2001) Treatment should be brief. There is also a post-op use. The addition of cyclobenzaprine to other agents is not recommended. (Clinical Pharmacology, 2008) Cyclobenzaprine-treated patients with fibromyalgia were 3 times as likely to report overall

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improvement and to report moderate reductions in individual symptoms, particularly sleep. (Tofferi, 2004) Note: Cyclobenzaprine is closely related to the tricyclic antidepressants, e.g., amitriptyline. See Antidepressants. Cyclobenzaprine is associated with a number needed to treat of 3 at 2 weeks for symptom improvement in LBP and is associated with drowsiness and dizziness. (Kinkade, 2007) Cyclobenzaprine is a skeletal muscle relaxant and a central nervous system (CNS) depressant that is marketed as Flexeril by Ortho McNeil Pharmaceutical.

## **Cymbalta® (duloxetine)**

Cymbalta® is the brand name for duloxetine, and it is supplied by Eli Lilly and Company. Duloxetine is an antidepressant in the class called Selective serotonin and norepinephrine reuptake inhibitors (SNRIs). See Duloxetine (Cymbalta®).

## **Cytokine DNA Testing for Pain**

Not recommended. There is no current evidence to support the use of cytokine DNA testing for the diagnosis of pain, including chronic pain. Scientific research on cytokines is rapidly evolving. There is vast and growing scientific evidence base concerning the biochemistry of inflammation and it is commonly understood that inflammation plays a key role in injuries and chronic pain. Cellular mechanisms are ultimately involved in the inflammatory process and healing, and the molecular machinery involves cellular signaling proteins or agents called cytokines. Given rapid developments in cytokine research, novel applications have emerged and one application is cytokine DNA signature testing which has been used as a specific test for certain pain diagnoses such as fibromyalgia or complex regional pain syndrome. The specific test for cytokine DNA testing is performed by the Cytokine Institute. ([www.cytokineinstitute.com](http://www.cytokineinstitute.com)) Two articles were found on the website. However, these articles did not meet the minimum standards for inclusion for evidence-based review. (Gavin, 2007) (Gillis, 2007)

## **Darvon® (propoxyphene)**

See Propoxyphene (Darvon®).

## **Demerol® (meperidine)**

See Meperidine (Demerol®).

## **Detoxification**

Recommended as indicated below. Detoxification is defined as withdrawing a person from a specific psychoactive substance, and it does not imply a diagnosis of addiction, abuse or misuse. May be necessary due to the following: (1) Intolerable side effects, (2) Lack of response, (3) Aberrant drug behaviors as related to abuse and dependence, (4) refractory comorbid psychiatric illness, or (5) Lack of functional improvement. Gradual weaning is recommended for long-term opioid users because opioids cannot be abruptly discontinued without probable risk of withdrawal symptoms. (Benzon, 2005) See also Rapid detox.

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## **Diagnostic criteria for CRPS**

See Complex Regional Pain Syndrome (CRPS), CRPS, diagnostic criteria.

## **Diclofenac (Voltaren®)**

See NSAIDs (non-steroidal anti-inflammatory drugs).

## **DMSO (dimethylsulfoxide)**

See Complex Regional Pain Syndrome (CRPS), CRPS, medications.

## **DNA testing**

See Cytokine DNA testing.

## **Dona™ glucosamine sulfate**

See Glucosamine (and Chondroitin Sulfate).

## **Dorsal column stimulators**

See Spinal Cord Stimulators (SCS).

## **Dronabinol**

See Cannabinoids.

## **Drug testing**

Recommended as an option, using a urine drug screen to assess for the use or the presence of illegal drugs. For more information, see Opioids, criteria for use: (2) Steps to Take Before a Therapeutic Trial of Opioids & (4) On-Going Management; Opioids, differentiation: dependence & addiction; Opioids, screening for risk of addiction (tests); & Opioids, steps to avoid misuse/addiction.

## **Drug therapy**

See Medications.

## **Duloxetine (Cymbalta®)**

Recommended as an option in first-line treatment option in neuropathic pain. Duloxetine (Cymbalta®) is a norepinephrine and serotonin reuptake inhibitor antidepressant (SNRIs). It has FDA approval for treatment of depression, generalized anxiety disorder, and for the treatment of pain related to diabetic neuropathy, with effect found to be significant by the end of week 1

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

(effect measured as a 30% reduction in baseline pain). The starting dose is 20-60 mg/day, and no advantage has been found by increasing the dose to twice a day, except in fibromyalgia. The medication has been found to be effective for treating fibromyalgia in women with and without depression, 60 mg once or twice daily. (Arnold, 2005) The most frequent side effects include nausea, dizziness and fatigue. GI symptoms are more common early in treatment. The side effect profile of Duloxetine is thought to be less bothersome to patients than that of tricyclic antidepressants. Note: On October 17, 2005, Eli Lilly and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of revision to the PRECAUTIONS/Hepatotoxicity section of the prescribing information for Cymbalta. Postmarketing reports of hepatic injury (including hepatitis and cholestatic jaundice) suggest that patients with preexisting liver disease who take duloxetine may have an increased risk for further liver damage. The new labeling extends the Precaution against using Cymbalta in patients with substantial alcohol use to include those patients with chronic liver disease. It is recommended that Cymbalta not be administered to patients with hepatic insufficiency. See also Antidepressants for chronic pain for general guidelines, as well as specific Duloxetine listing for more information and references. On June 13, 2008, the FDA approved a new indication for duloxetine HCl delayed-release capsules (Cymbalta®; Eli Lilly and Company) for the management of fibromyalgia in adults. The FDA notes that although duloxetine was effective for reducing pain in patients with and without major depressive disorder, the degree of pain relief may have been greater in those with comorbid depression. Treatment of fibromyalgia with duloxetine should be initiated at 30 mg/day for 1 week and then uptitrated to the recommended 60-mg dose. (Waknine, 2008) Note: This drug was recently included in a list of 20 medications identified by the FDA's Adverse Event Reporting System, that are under FDA investigation. (FDA, 2008)

### **Duragesic® (fentanyl transdermal system)**

Not recommended as a first-line therapy. Duragesic is the trade name of a fentanyl transdermal therapeutic system, which releases fentanyl, a potent opioid, slowly through the skin. It is manufactured by ALZA Corporation and marketed by Janssen Pharmaceutica (both subsidiaries of Johnson & Johnson). The FDA-approved product labeling states that Duragesic is indicated in the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by other means. See Fentanyl.

### **Dynatron STS**

See Transcutaneous electrotherapy.

### **Education**

Recommended. On-going education of the patient and family, as well as the employer, insurer, policy makers and the community should be the primary emphasis in the treatment of chronic pain. Currently, practitioners often think of education last, after medications, manual therapy and surgery. Practitioners must develop and implement an effective strategy and skills to educate patients, employers, insurance systems, policy makers and the community as a whole. An education-based paradigm should always start with inexpensive communication providing

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reassuring information to the patient. More in-depth education currently exists within a treatment regime employing functional restorative and innovative programs of prevention and rehabilitation. No treatment plan is complete without addressing issues of individual and/or group patient education as a means of facilitating self-management of symptoms and prevention. (Colorado, 2002) An educational technique known as the Alexander technique, along with exercise, is effective for long-term relief of chronic low back pain, according to the results of a randomized trial reported in the *BMJ*. Lessons in the Alexander technique offer an individualized approach designed to develop lifelong skills for self-care that help people avoid poor habits affecting posture and neuromuscular coordination. An accompanying editorial notes that the results of this study may not apply to clinical practice. In addition, in the US there are few instructors trained in this technique. (Little, 2008)

## **Effexor® (venlafaxine)**

Effexor® is the brand name for venlafaxine, and it is supplied by Wyeth Pharmaceuticals Inc. Venlafaxine is an antidepressant in the class called Selective serotonin and norepinephrine reuptake inhibitors (SNRIs). See Venlafaxine (Effexor®).

## **Electrical stimulators (E-stim)**

See specific individual treatment topics for treatment guidelines regarding the exact type of electrical stimulation treatment. The following are the choices:

- See Transcutaneous electrotherapy for
  - TENS, chronic pain (transcutaneous electrical nerve stimulation)
  - TENS, post operative pain (transcutaneous electrical nerve stimulation)
  - Electroceutical therapy (bioelectric nerve block)
  - Galvanic stimulation
  - Neuromuscular electrical stimulation (NMES)
  - H-wave stimulation (HWT)
  - Interferential current stimulation (ICS)
  - Microcurrent electrical stimulation (MENS devices)
  - RS-4i sequential stimulator
  - Sympathetic therapy
  - Dynatron STS
- Percutaneous electrical nerve stimulation (PENS)
- Percutaneous neuromodulation therapy (PNT)
- Spinal cord stimulation

## **Electroceutical therapy (bioelectric nerve block)**

See Transcutaneous electrotherapy.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Epidural steroid injections (ESIs)

Recommended as an option for treatment of radicular pain (defined as pain in dermatomal distribution with corroborative findings of radiculopathy). See specific criteria for use below. Most current guidelines recommend no more than 2 ESI injections. This is in contradiction to previous generally cited recommendations for a “series of three” ESIs. These early recommendations were primarily based on anecdotal evidence. Research has now shown that, on average, less than two injections are required for a successful ESI outcome. Current recommendations suggest a second epidural injection if partial success is produced with the first injection, and a third ESI is rarely recommended. Epidural steroid injection can offer short term pain relief and use should be in conjunction with other rehab efforts, including continuing a home exercise program. There is little information on improved function. The American Academy of Neurology recently concluded that epidural steroid injections may lead to an improvement in radicular lumbosacral pain between 2 and 6 weeks following the injection, but they do not affect impairment of function or the need for surgery and do not provide long-term pain relief beyond 3 months, and there is insufficient evidence to make any recommendation for the use of epidural steroid injections to treat radicular cervical pain. (Armon, 2007) See also Epidural steroid injections, “series of three.”

### Criteria for the use of Epidural steroid injections:

*Note: The purpose of ESI is to reduce pain and inflammation, restoring range of motion and thereby facilitating progress in more active treatment programs, and avoiding surgery, but this treatment alone offers no significant long-term functional benefit.*

- 1) Radiculopathy must be documented by physical examination and corroborated by imaging studies and/or electrodiagnostic testing.
- 2) Initially unresponsive to conservative treatment (exercises, physical methods, NSAIDs and muscle relaxants).
- 3) Injections should be performed using fluoroscopy (live x-ray) for guidance.
- 4) If used for diagnostic purposes, a maximum of two injections should be performed. A second block is not recommended if there is inadequate response to the first block. Diagnostic blocks should be at an interval of at least one to two weeks between injections.
- 5) No more than two nerve root levels should be injected using transforaminal blocks.
- 6) No more than one interlaminar level should be injected at one session.
- 7) In the therapeutic phase, repeat blocks should be based on continued objective documented pain and functional improvement, including at least 50% pain relief with associated reduction of medication use for six to eight weeks, with a general recommendation of no more than 4 blocks per region per year. (Manchikanti, 2003) (CMS, 2004) (Boswell, 2007)
- 8) Current research does not support a “series-of-three” injections in either the diagnostic or therapeutic phase. We recommend no more than 2 ESI injections.

## Exercise

Recommended. There is strong evidence that exercise programs, including aerobic conditioning and strengthening, are superior to treatment programs that do not include exercise. There is no sufficient evidence to support the recommendation of any particular exercise regimen over any

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

other exercise regimen. A therapeutic exercise program should be initiated at the start of any treatment or rehabilitation program, unless exercise is contraindicated. Such programs should emphasize education, independence, and the importance of an on-going exercise regime. (State, 2002) (Airaksinen, 2006) A recent study of the long term impact of aerobic exercise on musculoskeletal pain, in a prospective cohort of 866 healthy seniors followed for 14 years, found that exercise was associated with a substantial and significant reduction in pain even after adjusting for gender, baseline BMI and attrition, and despite the fact that fractures, a significant predictor of pain, were slightly more common among exercisers. (Bruce, 2005) A recent trial concluded that active physical treatment, cognitive-behavioral treatment, and the two combined each resulted in equally significant improvement, much better compared to no treatment. (The cognitive treatment focused on encouraging increased physical activity.) (Smeets, 2006) Progressive walking, simple strength training, and stretching improved functional status, key symptoms, and self-efficacy in patients with fibromyalgia. (Rooks, 2007) Physical conditioning in chronic pain patients can have immediate and long-term benefits, according to a low-quality study presented at the American Academy of Pain Medicine 24th Annual Meeting. (Burlerson, 2008) Physical therapy in warm-water has been effective and highly recommended in persons with fibromyalgia. In this RCT, an aquatic exercise program including one-hour, supervised, water-based exercise sessions, three times per week for 8 months, was found to be cost-effective in terms of both health care costs and societal costs. (Gusi, 2008) An educational technique known as the Alexander technique, along with exercise, is effective for long-term relief of chronic low back pain, according to the results of a randomized trial reported in the BMJ. (Little, 2008)

### **Fentanyl**

Fentanyl is an opioid analgesic with a potency eighty times that of morphine. Weaker opioids are less likely to produce adverse effects than stronger opioids such as fentanyl. For more information and references, see Opioids. See also Actiq® (fentanyl lollipop); Duragesic® (fentanyl transdermal system); & Fentora® (fentanyl buccal tablet).

### **Fentora® (fentanyl buccal tablet)**

Not recommended for musculoskeletal pain. Fentora is an opioid painkiller currently approved for the treatment of breakthrough pain in certain cancer patients. Cephalon had applied to the FDA for approval to market the drug for patients with other pain conditions such as chronic low back pain and chronic neuropathic pain, but approval was not obtained. See Opioids.

### **Fioricet**

See Barbiturate-containing analgesic agents (BCAs).

### **Fish oil**

See Cod liver oil.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Flexeril® (Cyclobenzaprine)

See Cyclobenzaprine (Flexeril®).

## fMRI (functional magnetic resonance imaging)

See Functional imaging of brain responses to pain & Functional MRI.

## Functional imaging of brain responses to pain

Not recommended. Functional neuroimaging is helping to identify the sensory and emotional components of pain and its autonomic responses, and may help in the design of more rational treatments for pain. However, this test is only useful in a research setting at this time and does not have a role in the evaluation or treatment of patients. Specifically, functional magnetic resonance imaging (fMRI) may have an important role in improved therapeutic approaches to pain. Physiological studies of pain have found numerous regions of the brain to be involved in the interpretation of the 'pain experience'; studies in chronic pain conditions have identified a significant CNS component; and fMRI studies of surrogate models of chronic pain are also being used to further this understanding. (Peyron, 2000) (Mackey, 2004) (Borsook, 2006) (Prager, 2007) Conditions such as depression, anxiety, sleep disturbances, and decision-making difficulties, which affect the quality of life of chronic pain patients as much as the pain itself, may be directly related to altered brain function as a result of chronic pain. (Baliki, 2008)

## Functional improvement measures

Recommended. The importance of an assessment is to have a measure that can be used repeatedly over the course of treatment to demonstrate improvement of function, or maintenance of function that would otherwise deteriorate. It should include the following categories:

*Work Functions and/or Activities of Daily Living, Self Report of Disability* (e.g., walking, driving, keyboard or lifting tolerance, Oswestry, pain scales, etc): Objective measures of the patient's functional performance in the clinic (e.g., able to lift 10 lbs floor to waist x 5 repetitions) are preferred, but this may include self-report of functional tolerance and can document the patient self-assessment of functional status through the use of questionnaires, pain scales, etc (Oswestry, DASH, VAS, etc.)

*Physical Impairments* (e.g., joint ROM, muscle flexibility, strength, or endurance deficits): Include objective measures of clinical exam findings. ROM should be in documented in degrees.

*Approach to Self-Care and Education* Reduced Reliance on Other Treatments, Modalities, or Medications: This includes the provider's assessment of the patient compliance with a home program and motivation. The provider should also indicate a progression of care with increased active interventions (vs. passive interventions) and reduction in frequency of treatment over course of care. (California, 2007)

For chronic pain, also consider return to normal quality of life, e.g., go to work/volunteer each day; normal daily activities each day; have a social life outside of work; take an active part in family life. (Cowan, 2008)

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Functional MRI

Not recommended. Functional neuroimaging is helping to identify the sensory and emotional components of pain and its autonomic responses, and may help in the design of more rational treatments for pain. However, this test is only useful in a research setting at this time and does not have a role in the evaluation or treatment of patients. There are no studies about the use of functional MRI in a clinical setting. (Borsook2, 2000)

## Functional restoration programs (FRPs)

Recommended, although research is still ongoing as to how to most appropriately screen for inclusion in these programs. Functional restoration programs (FRPs), a type of treatment included in the category of interdisciplinary pain programs (see Chronic pain programs), were originally developed by Mayer and Gatchel. FRPs were designed to use a medically directed, interdisciplinary pain management approach geared specifically to patients with chronic disabling occupational musculoskeletal disorders. These programs emphasize the importance of function over the elimination of pain. FRPs incorporate components of exercise progression with disability management and psychosocial intervention. Long-term evidence suggests that the benefit of these programs diminishes over time, but still remains positive when compared to cohorts that did not receive an intensive program. (Bendix, 1998) A Cochrane review suggests that there is strong evidence that intensive multidisciplinary rehabilitation with functional restoration reduces pain and improves function of patients with low back pain. The evidence is contradictory when evaluating the programs in terms of vocational outcomes. (Guzman 2001) It must be noted that all studies used for the Cochrane review excluded individuals with extensive radiculopathy, and several of the studies excluded patients who were receiving a pension, limiting the generalizability of the above results. Studies published after the Cochrane review also indicate that intensive programs show greater effectiveness, in particular in terms of return to work, than less intensive treatment. (Airaksinen, 2006) There appears to be little scientific evidence for the effectiveness of multidisciplinary biopsychosocial rehabilitation compared with other rehabilitation facilities for neck and shoulder pain, as opposed to low back pain and generalized pain syndromes. (Karjalainen, 2003) Treatment is not suggested for longer than 2 weeks without evidence of demonstrated efficacy as documented by subjective and objective gains. For general information see Chronic pain programs.

## Gabapentin (Neurontin®)

Gabapentin is an anti-epilepsy drug (AEDs - also referred to as anti-convulsants), which has been shown to be effective for treatment of diabetic painful neuropathy and postherpetic neuralgia and has been considered as a first-line treatment for neuropathic pain. See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Gabapentin listing for more information and references.

## Galvanic Stimulation

See Transcutaneous electrotherapy.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Glucosamine (and Chondroitin Sulfate)

Recommended as an option given its low risk, in patients with moderate arthritis pain, especially for knee osteoarthritis. Studies have demonstrated a highly significant efficacy for crystalline glucosamine sulphate (GS) on all outcomes, including joint space narrowing, pain, mobility, safety, and response to treatment, but similar studies are lacking for glucosamine hydrochloride (GH). (Richy, 2003) (Ruane, 2002) (Towheed-Cochrane, 2001) (Braham, 2003) (Reginster, 2007) A randomized, doubleblind placebo controlled trial, with 212 patients, found that patients on placebo had progressive joint-space narrowing, but there was no significant joint-space loss in patients on glucosamine sulphate. (Reginster, 2001) Another RCT with 202 patients concluded that long-term treatment with glucosamine sulfate retarded the progression of knee osteoarthritis, possibly determining disease modification. (Pavelka, 2002) The Glucosamine Chondroitin Arthritis Intervention Trial (GAIT) funded by the National Institutes of Health concluded that glucosamine hydrochloride (GH) and chondroitin sulfate were not effective in reducing knee pain in the study group overall; however, these may be effective in combination for patients with moderate-to-severe knee pain. [Note: The GAIT investigators did not use glucosamine sulfate (GS).] (Distler, 2006) Exploratory analyses suggest that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain. (Clegg, 2006) In a recent meta-analysis, the authors found that the apparent benefits of chondroitin were largely confined to studies of poor methodological quality, such as those with small patient numbers or ones with unclear concealment of allocation. When the analysis was limited to the three best-designed studies with the largest sample sizes (40% of all patients), chondroitin offered virtually no relief from joint pain. While not particularly effective, chondroitin use did not appear to be harmful either, according to a meta-analysis of 12 of the studies. (Reichenbach, 2007) Despite multiple controlled clinical trials of glucosamine in osteoarthritis (mainly of the knee), controversy on efficacy related to symptomatic improvement continues. Differences in results originate from the differences in products, study design and study populations. Symptomatic efficacy described in multiple studies performed with glucosamine sulphate (GS) support continued consideration in the OA therapeutic armamentarium. Compelling evidence exists that GS may reduce the progression of knee osteoarthritis. Results obtained with GS may not be extrapolated to other salts (hydrochloride) or formulations (OTC or food supplements) in which no warranty exists about content, pharmacokinetics and pharmacodynamics of the tablets. (Reginster, 2007) [Note: DONA™ Glucosamine Sulfate is the original crystalline glucosamine sulfate (GS), which was first developed and marketed for human use by Rotta Research Laboratorium, funding some of the initial trials. Glucosamine hydrochloride (GH) is not proprietary, so it tends to be less expensive but there has also been less funding for quality studies.]

*Recent research:* This RCT assessed radiographic outcomes in OA of the knee in patients being treated with glucosamine hydrochloride (note: GH not GS), chondroitin sulfate (CS), glucosamine plus CS, celecoxib, or placebo. Over 2 years, no treatment achieved the predefined clinically important difference from placebo in terms of joint space width (JSW) loss. The effect of the combination of glucosamine plus CS may be less active than the effect of each treatment singly. Kellgren/Lawrence (K/L) grade 2 knees may represent a more potentially responsive population. Treatment effects on K/L grade 2 knees (less severe OA), but not on K/L grade 3 knees (more severe), showed a trend toward improvement relative to the placebo group. (Sawitzke, 2008)

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## **Green tea [DWC]**

Green Tea is not recommended for chronic pain.

## **Herbal medicines [DWC]**

See specific Sections on Boswellia Serrata Resin (Frankincense), Cannabinoids, Curcumin (tumeric), Green Tea, Pycnogenol (maritime pine bark), Uncaria Tomentosa (Cat's Claw), White willow bark.

## **Home health services**

Recommended only for otherwise recommended medical treatment for patients who are homebound, on a part-time or “intermittent” basis, generally up to no more than 35 hours per week. Medical treatment does not include homemaker services like shopping, cleaning, and laundry, and personal care given by home health aides like bathing, dressing, and using the bathroom when this is the only care needed. (CMS, 2004)

## **Honey & cinnamon [DWC]**

Honey and cinnamon are not recommended for chronic pain.

## **Horizontal therapy (HT)**

See Interferential current stimulation (ICS).

## **H-Wave stimulation (HWT)**

See Transcutaneous electrotherapy.

## **Hydrocodone (Vicodin®, Lortab®)**

Hydrocodone is a semi-synthetic opioid which is considered the most potent oral opioid that does not require special documentation for prescribing in some states (not including California). See Opioids.

## **Hydromorphone (Dilaudid®)**

See Opioids. See also Intrathecal drug delivery systems, medications.

## **Ibuprofen**

See Anti-inflammatory medications.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Imaging

See Functional imaging of brain responses to pain.

## Implantable drug-delivery systems (IDDSs)

Recommended only as an end-stage treatment alternative for selected patients for specific conditions indicated below, after failure of at least 6 months of less invasive methods, and following a successful temporary trial. Results of studies of opioids for musculoskeletal conditions (as opposed to cancer pain) generally recommend short use of opioids for severe cases, not to exceed 2 weeks, and do not support chronic use (for which a pump would be used), although IDDSs may be appropriate in selected cases of chronic, severe low back pain or failed back syndrome. This treatment should only be used relatively late in the treatment continuum, when there is little hope for effective management of chronic intractable pain from other therapies. (Angel, 1998) (Kumar, 2002) (Hassenbusch, 2004) (Boswell, 2005) For most patients, it should be used as part of a program to facilitate restoration of function and return to activity, and not just for pain reduction. The specific criteria in these cases include the failure of at least 6 months of other conservative treatment modalities, intractable pain secondary to a disease state with objective documentation of pathology, further surgical intervention is not indicated, psychological evaluation unequivocally states that the pain is not psychological in origin, and a temporary trial has been successful prior to permanent implantation as defined by a 50% reduction in pain. (Tutak, 1996) (Yoshida, 1996) (BlueCross, 2005) (United Health Care, 2005) See also Opioids. In a study of IDDS in 136 patients with low back pain, after one year 87% of the patients described their quality of life as fair to excellent, and 87% said they would repeat the implant procedure. However, complication rates (i.e., infection, dislodging, and cerebrospinal fluid leak) are likely to rise with time in these procedures and more longitudinal outcome studies need to be conducted. (Deer, 2004) In one survey involving 429 patients with nonmalignant pain treated with intrathecal therapy, physician reports of global pain relief scores were excellent in 52.4% of patients, good in 42.9%, and poor in 4.8%. In another study of 120 patients, the mean pain intensity score had fallen from 93.6 to 30.5 six months after initiation of therapy. In both studies, patients reported significant improvement in activities of daily living, quality of life measures, and satisfaction with the therapy. Constipation, urinary retention, nausea, vomiting, and pruritus are typical early adverse effects of intrathecal morphine and are readily managed symptomatically. Other potential adverse effects include amenorrhea, loss of libido, edema, respiratory depression, and technical issues with the intrathecal system. (Winkelmuller, 1996) (Paice, 1997) One study in patients suffering from chronic low back pain caused by failed back syndrome found a 27% improvement after 5 years for patients in the intrathecal drug therapy group, compared with a 12% improvement in the control group. (Kumar, 2002) Supporting empirical evidence is significantly supplemented and enhanced when combined with the individually based observational evidence gained through an individual trial prior to implant. This individually based observational evidence should be used to demonstrate effectiveness and to determine appropriate subsequent treatment. Generally, use of implantable pumps is FDA approved and indicated for chronic intractable pain. Treatment conditions may include FBSS, CRPS, Arachnoiditis, Diffuse Cancer Pain, Osteoporosis, and Axial Somatic Pain. As we have gained more experience with this therapy, it has become apparent that even intrathecal opiates, when administered in the long term, can be associated with problems such as

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

tolerance, hyperalgesia, and other side effects. Consequently, long-term efficacy has not been convincingly proven. However, it is important to note that there is a distinction between "tolerance" and "addiction", and the levels of drugs administered intrathecally should be significantly below what might be needed orally in their absence. (Osenbach, 2001) (BlueCross BlueShield, 2005) See also Intrathecal drug delivery systems, medications.

*Refills:* IDDSs dispense drugs according to instructions programmed by the clinician to deliver a specific amount of drug per day or to deliver varying regimens based on flexible programming options, and the pump may need to be refilled at regular intervals. The time between refills will vary based on pump reservoir size, drug concentration, dose, and flow rate. A programming session, which may occur along with or independent of a refill session, allows the clinician to adjust the patient's prescription as well as record or recall important information about the prescription. (Hassenbusch, 2004)

### **Indications for Implantable drug-delivery systems:**

Implantable infusion pumps are considered medically necessary when used to deliver drugs for the treatment of:

- o Primary liver cancer (intrahepatic artery injection of chemotherapeutic agents);
- o Metastatic colorectal cancer where metastases are limited to the liver (intrahepatic artery injection of chemotherapeutic agents);
- o Head/neck cancers (intra-arterial injection of chemotherapeutic agents);
- o Severe, refractory spasticity of cerebral or spinal cord origin in patients who are unresponsive to or cannot tolerate oral baclofen (Lioresal®) therapy (intrathecal injection of baclofen)

Permanently implanted intrathecal (intraspinal) infusion pumps for the administration of opiates or non-opiate analgesics, in the treatment of chronic intractable pain, are considered medically necessary when:

- Used for the treatment of malignant (cancerous) pain and all of the following criteria are met:
  1. Strong opioids or other analgesics in adequate doses, with fixed schedule (not PRN) dosing, have failed to relieve pain or intolerable side effects to systemic opioids or other analgesics have developed; and
  2. Life expectancy is greater than 3 months (less invasive techniques such as external infusion pumps provide comparable pain relief in the short term and are consistent with standard of care); and
  3. Tumor encroachment on the thecal sac has been ruled out by appropriate testing; and
  4. No contraindications to implantation exist such as sepsis or coagulopathy; and
  5. A temporary trial of spinal (epidural or intrathecal) opiates has been successful prior to permanent implantation as defined by a 50% reduction in pain. A *temporary* trial of intrathecal (intraspinal) infusion pumps is considered medically necessary only when criteria 1-4 above are met.
- Used for the treatment of non-malignant (non-cancerous) pain with a duration of greater than 6 months and all of the following criteria are met:

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

1. Documentation, in the medical record, of the failure of 6 months of other conservative treatment modalities (pharmacologic, surgical, psychologic or physical), if appropriate and not contraindicated; and
2. Intractable pain secondary to a disease state with objective documentation of pathology in the medical record; and
3. Further surgical intervention or other treatment is not indicated or likely to be effective; and
4. Psychological evaluation has been obtained and evaluation states that the pain is not primarily psychologic in origin and that benefit would occur with implantation despite any psychiatric comorbidity; and
5. No contraindications to implantation exist such as sepsis or coagulopathy; and
6. A temporary trial of spinal (epidural or intrathecal) opiates has been successful prior to permanent implantation as defined by at least a 50% to 70% reduction in pain and documentation in the medical record of functional improvement and associated reduction in oral pain medication use. A temporary trial of intrathecal (intraspinous) infusion pumps is considered medically necessary only when criteria 1-5 above are met.

## **Implantable spinal cord stimulators**

See Spinal Cord Stimulators (SCS).

## **Injection with anaesthetics and/or steroids**

See more specific modality. The following are choices: Epidural steroid injections (ESI's), Lumbar sympathetic block; Trigger point injections; Stellate ganglion block; Prolotherapy.

## **Interdisciplinary rehabilitation programs**

See Chronic pain programs.

## **Interferential Current Stimulation (ICS)**

See Transcutaneous electrotherapy

## **Intrathecal drug delivery systems (IDDSs)**

See Implantable drug-delivery systems (IDDSs).

## **Intrathecal drug delivery systems, medications**

Recommended as indicated below.

*Recommended 1st stage:* Morphine is generally the initial IDDS medication. The maximum recommended dose for this drug is 15 mg/day with a concentration of 20 mg/mL. An alternative non-FDA approved medication is hydromorphone. The maximum recommended dose for this medication is 4 mg/day with a concentration of 10 mg/mL. Other opioids (including Fentanyl

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and Sufentanil) have been used for intrathecal chronic non-malignant pain but are non-FDA approved and have little research associated with their use. (Waara-Wolleat, 2006) (Deer, 2007) The previous 2003 Polyanalgesic conference recommended a maximum dose of intrathecal morphine at 15 mg/day with a maximum concentration of 30 mg/mL. They also recommended a maximum dose of hydromorphone of 10 mg/day with a concentration of 30 mg/mL. (Hassenbusch, 2004) It can be seen that there has been a substantial decrease in concentration (particularly for hydromorphone). The newer maximum concentrations were recommended, in part, to prevent granulomas.

*Recommended 2nd stage:* If side effects occur, an upper limit of dosing is reached, or neuropathic pain is present, clonidine is next recommended as an addition to an opioid (maximum recommended dose of 1 mg/day and a concentration of 2 mg/mL). Bupivacaine has also been recommended as an alternative to clonidine (maximum dose of 30 mg/day and a concentration of 40 mg/mL). Clonidine, which is FDA approved for intrathecal delivery, is thought to provide analgesic effect via a non-opioid mechanism. It has been found to offer only short-term relief when used as a single agent. (Deer, 2007)

*Recommended 3rd stage:* The recommendation has been made to add both clonidine and bupivacaine. Baclofen has been used to treat intractable spasticity from brain injury, cerebral palsy, and spinal cord injury and has resulted in improvement in muscle tone and pain relief. (Guillaume, 2005) See also Ziconotide (Prialt®), which is recommended after documentation of a failure of a trial of intrathecal morphine or hydromorphone (Dilaudid). The 2007 Polyanalgesic Consensus Conference Recommendations for the Management of Pain by Intrathecal Drug Delivery concluded that ziconotide should be updated to a first-line intrathecal drug. This recommendation was published in a journal not yet accepted for inclusion in MEDLINE and the conference was sponsored by Elan Pharmaceuticals. (Deer, 2007)

### **Intrathecal pumps**

See Implantable drug-delivery systems (IDDSs).

### **Intravenous regional sympathetic blocks (for RSD/CRPS, nerve blocks)**

Not recommended, except as indicated below when other treatments are contraindicated. For detailed recommendations by type of block, see Regional sympathetic blocks (stellate ganglion block, thoracic sympathetic block, & lumbar sympathetic block). One meta-analysis found that no significant difference was found between guanethidine and placebo on any of the outcome measures and in one case the trial was stopped prematurely because of the severity of the adverse effects. (Jadad, 1995). Another randomized controlled trial of 32 patients found that IV clodronate is better than placebo and induces lasting improvement of RSD/CRPS. (Varena, 2000) A randomized controlled trial using guanethidine found that guanethidine was no better than the placebo in improving pain scores in RSD/CRPS. (Ramamurthy, 1995) Since there is a trial suggesting benefit from intravenous regional sympathetic blocks, while not recommended, if other treatments are contraindicated (e.g. when a stellate ganglion block cannot be done due to bleeding diathesis), intravenous regional blocks may be performed. IV regional blocks, also known as Bier blocks, are not commonly done for RSD/CRPS. Although there is very limited scientific evidence to support this treatment, it is recommended as an option in certain cases when there are no other alternatives. When the procedure is performed, it must be done in

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conjunction with a rehabilitation program. There is no role for intravenous regional sympathetic blocks for the diagnosis of RSD/CRPS. (Ramamurthy2, 1995) (Jadad2, 1995).

## **Kadian® (morphine sulfate)**

Kadian® is a brand of morphine sulfate, supplied by Alpharma Pharmaceuticals. See Opioids for recommendations and references.

## **Ketamine**

Not recommended. There is insufficient evidence to support the use of ketamine for the treatment of chronic pain. There are no quality studies that support the use of ketamine for chronic pain, but it is under study for CRPS. (Goldberg2, 2005) (Grant, 1981) (Rabben, 1999) Ketamine is an anesthetic in animals and humans, and also a drug of abuse in humans, but ketamine may offer a promising therapeutic option in the treatment of appropriately selected patients with intractable CRPS. More study is needed to further establish the safety and efficacy of this drug. (Correll, 2004) One very small study concluded that ketamine showed a significant analgesic effect on peripheral neuropathic pain, but the clinical usefulness is limited by disturbing side effects. Another study by the same author with a sample size too small for ODG (10) concluded that ketamine showed a significant analgesic effect in patients with neuropathic pain after spinal cord injury, but ketamine was associated with frequent side effects. (Kvarnström, 2003-4)

## **Ketoprofen**

See NSAIDs (non-steroidal anti-inflammatory drugs).

## **Lamotrigine (Lamictal®)**

See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Lamotrigine listing.

## **Levetiracetam (Keppra®)**

See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Levetiracetam Listing listing.

## **Lidocaine (anesthetic)**

Lidocaine is a local anesthetic. See CRPS, medications; CRPS, sympathetic and epidural blocks; Topical analgesics.

## **Lidoderm® (lidocaine patch)**

Lidoderm® is the brand name for a lidocaine patch produced by Endo Pharmaceuticals. Topical lidocaine may be recommended for localized peripheral pain after there has been evidence of a trial of first-line therapy (tri-cyclic or SNRI anti-depressants or an AED such as gabapentin or

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Lyrica). This is not a first-line treatment and is only FDA approved for post-herpetic neuralgia. Further research is needed to recommend this treatment for chronic neuropathic pain disorders other than post-herpetic neuralgia. Formulations that do not involve a dermal-patch system are generally indicated as local anesthetics and anti-pruritics. For more information and references, see Topical analgesics.

### **Low-Level Laser Therapy (LLLT)**

Not recommended. There has been interest in using low-level lasers as a conservative alternative to treat pain. Low-level lasers, also known as "cold lasers" and non-thermal lasers, refer to the use of red-beam or near-infrared lasers with a wavelength between 600 and 1000 nm and wattage from 5-500 milliwatts. (In contrast, lasers used in surgery typically use 300 Watts.) When applied to the skin, these lasers produce no sensation and do not burn the skin. Because of the low absorption by human skin, it is hypothesized that the laser light can penetrate deeply into the tissues where it has a photobiostimulative effect. One low-level laser device, the MicroLight 830 Laser, has received clearance for marketing from the U.S. Food and Drug Administration (FDA) specifically for the treatment of carpal tunnel syndrome. Other protocols have used low-level laser energy applied to acupuncture points on the fingers and hand. This technique may be referred to as "laser acupuncture." Given the equivocal or negative outcomes from a significant number of randomized clinical trials, it must be concluded that the body of evidence does not allow conclusions other than that the treatment of most pain syndromes with low level laser therapy provides at best the equivalent of a placebo effect. (Naeser, 2002) (Gur, 2002) (Basford, 1999) (Conti, 1997) (de Bie, 1998) (BlueCross BlueShield, 2005) Low Level Laser Therapy (LLLT) was introduced as an alternative non-invasive treatment for Osteoarthritis (OA) about 20 years ago, but its effectiveness is still controversial. For OA, the results are conflicting in different studies and may depend on the method of application and other features of the LLLT application. Despite some positive findings, data is lacking on how LLLT effectiveness is affected by four important factors: wavelength, treatment duration of LLLT, dosage and site of application over nerves instead of joints. There is clearly a need to investigate the effects of these factors on LLLT effectiveness for OA in randomized controlled clinical trials. (Brosseau-Cochrane, 2004) This meta-analysis concluded that there are insufficient data to draw firm conclusions about the effects of LLLT for low-back pain compared to other treatments, different lengths of treatment, different wavelengths and different dosages. (Yousefi-Nooraie-Cochrane, 2007)

### **Lumbar sympathetic block**

Recommended as indicated below. Useful for diagnosis and treatment of pain of the pelvis and lower extremity secondary to CRPS-I and II. This block is commonly used for differential diagnosis and is the preferred treatment of sympathetic pain involving the lower extremity. For diagnostic testing, use three blocks over a 3-14 day period. For a positive response, pain relief should be 50% or greater for the duration of the local anesthetic and pain relief should be associated with functional improvement. Should be followed by intensive physical therapy. (Colorado, 2002)

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## Lymph drainage therapy

Not recommended. Manual lymphatic drainage therapy, as performed by massage therapists, is intended to stimulate or move excess fluid away from the swollen area so that it can drain away normally. As a treatment for chronic pain, there is no good evidence to support its use. The results of this RCT indicate that, during the first 6 months of complex regional pain syndrome type I, manual lymph drainage provides no additional benefit when applied in conjunction with an intensive exercise program. (Uher, 2000)

## Lyrica® (pregabalin)

Lyrica® is the brandname for pregabalin, and it is produced by Pfizer. See Pregabalin (Lyrica®).

## Magnet Therapy

Not recommended. Biomagnetic therapy is considered investigational. The data from randomized, placebo-controlled clinical trials fails to demonstrate that biomagnetic therapy results in improved health outcomes for any type of pain. Biomagnetic therapy has been proposed for the relief of chronic painful conditions; it is proposed that magnets, worn close to the skin, create an electromagnetic field within the body that suppresses pain. The theory is that the magnetic field causes potassium channels to be stimulated, producing repolarization or hyperpolarization. Biomagnetic therapy has been investigated for various types of pain, including peripheral neuropathy, chronic low back pain, carpal tunnel syndrome, plantar heel pain and hip and knee pain due to osteoarthritis. (Collacott-*JAMA*, 2000) (BlueCross BlueShield, 2005)

## Manual therapy & manipulation

Recommended for chronic pain if caused by musculoskeletal conditions. Manual Therapy is widely used in the treatment of musculoskeletal pain. The intended goal or effect of Manual Medicine is the achievement of positive symptomatic or objective measurable gains in functional improvement that facilitate progression in the patient's therapeutic exercise program and return to productive activities. Manipulation is manual therapy that moves a joint beyond the physiologic range-of-motion but not beyond the anatomic range-of-motion.

**Low back:** Recommended as an option. *Therapeutic care* – Trial of 6 visits over 2 weeks, with evidence of objective functional improvement, total of up to 18 visits over 6-8 weeks. *Elective/maintenance care* – Not medically necessary. *Recurrences/flare-ups* – Need to re-evaluate treatment success, if RTW achieved then 1-2 visits every 4-6 months.

**Ankle & Foot:** Not recommended.

**Carpal tunnel syndrome:** Not recommended.

**Forearm, Wrist, & Hand:** Not recommended.

**Knee:** Not recommended.

### Treatment Parameters from state guidelines

a. Time to produce effect: 4 to 6 treatments

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b. Frequency: 1 to 2 times per week the first 2 weeks, as indicated by the severity of the condition. Treatment may continue at 1 treatment per week for the next 6 weeks.

c. Maximum duration: 8 weeks. At week 8, patients should be reevaluated. Care beyond 8 weeks may be indicated for certain chronic pain patients in whom manipulation is helpful in improving function, decreasing pain and improving quality of life. In these cases, treatment may be continued at 1 treatment every other week until the patient has reached plateau and maintenance treatments have been determined. Extended durations of care beyond what is considered “maximum” may be necessary in cases of re-injury, interrupted continuity of care, exacerbation of symptoms, and in those patients with comorbidities. Such care should be re-evaluated and documented on a monthly basis. Treatment beyond 4-6 visits should be documented with objective improvement in function. Palliative care should be reevaluated and documented at each treatment session. (Colorado, 2006) Injured workers with complicating factors may need more treatment, if documented by the treating physician.

*Number of Vists:* Several studies of manipulation have looked at duration of treatment, and they generally showed measured improvement within the first few weeks or 3-6 visits of chiropractic treatment, although improvement tapered off after the initial sessions. If chiropractic treatment is going to be effective, there should be some outward sign of subjective or objective improvement within the first 6 visits.

*Active Treatment versus Passive Modalities:* Manipulation is a passive treatment, but many chiropractors also perform active treatments, and these recommendations are covered under Physical therapy (PT), as well as Education and Exercise. The use of active treatment modalities instead of passive treatments is associated with substantially better clinical outcomes. (Fritz, 2007) Active treatments also allow for fading of treatment frequency along with active self-directed home PT, so that less visits would be required in uncomplicated cases.

*Current Research:* A recent comprehensive meta-analysis of all clinical trials of manipulation for low back conditions has concluded that there was good evidence for its use in chronic low back pain, while the evidence for use in radiculopathy was not as strong, but still positive. (Lawrence, 2008) A Delphi consensus study based on this meta-analysis has made some recommendations regarding chiropractic treatment frequency and duration for low back conditions. They recommend an initial trial of 6-12 visits over a 2-4 week period, and, at the midway point as well as at the end of the trial, there should be a formal assessment whether the treatment is continuing to produce satisfactory clinical gains. If the criteria to support continuing chiropractic care (substantive, measurable functional gains with remaining functional deficits) have been achieved, a follow-up course of treatment may be indicated consisting of another 4-12 visits over a 2-4 week period. According to the study, “One of the goals of any treatment plan should be to reduce the frequency of treatments to the point where maximum therapeutic benefit continues to be achieved while encouraging more active self-therapy, such as independent strengthening and range of motion exercises, and rehabilitative exercises. Patients also need to be encouraged to return to usual activity levels despite residual pain, as well as to avoid catastrophizing and overdependence on physicians, including doctors of chiropractic.” (Globe, 2008) These recommendations are consistent with the recommendations in ODG, which suggest a trial of 6 visits, and then 12 more visits (for a total of 18) based on the results of the trial, except that the Delphi recommendations in effect incorporate two trials, with a total of up to 12 trial visits with a re-evaluation in the middle, before also continuing up to 12 more visits (for a total of up to 24). Payors may want to consider this option for patients showing continuing improvement, based on

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documentation at two points during the course of therapy, allowing 24 visits in total, especially if the documentation of improvement has shown that the patient has achieved or maintained RTW.

## **Marijuana**

See Cannabinoids.

## **Massage therapy**

Recommended as an option as indicated below. This treatment should be an adjunct to other recommended treatment (e.g. exercise), and it should be limited to 4-6 visits in most cases. Scientific studies show contradictory results. Furthermore, many studies lack long-term follow-up. Massage is beneficial in attenuating diffuse musculoskeletal symptoms, but beneficial effects were registered only during treatment. Massage is a passive intervention and treatment dependence should be avoided. This lack of long-term benefits could be due to the short treatment period or treatments such as these do not address the underlying causes of pain. (Hasson, 2004) A very small pilot study showed that massage can be at least as effective as standard medical care in chronic pain syndromes. Relative changes are equal, but tend to last longer and to generalize more into psychologic domains. (Walach 2003) The strongest evidence for benefits of massage is for stress and anxiety reduction, although research for pain control and management of other symptoms, including pain, is promising. The physician should feel comfortable discussing massage therapy with patients and be able to refer patients to a qualified massage therapist as appropriate. (Corbin 2005) Massage is an effective adjunct treatment to relieve acute postoperative pain in patients who had major surgery, according to the results of a randomized controlled trial recently published in the *Archives of Surgery*. (Mitchinson, 2007)

## **Medications for chronic pain**

Recommended as indicated below. Relief of pain with the use of medications is generally temporary, and measures of the lasting benefit from this modality should include evaluating the effect of pain relief in relationship to improvements in function and increased activity. Before prescribing any medication for pain the following should occur: (1) determine the aim of use of the medication; (2) determine the potential benefits and adverse effects; (3) determine the patient's preference. Only one medication should be given at a time, and interventions that are active and passive should remain unchanged at the time of the medication change. A trial should be given for each individual medication. Analgesic medications should show effects within 1 to 3 days, and the analgesic effect of antidepressants should occur within 1 week. A record of pain and function with the medication should be recorded. (Mens, 2005) The recent AHRQ review of comparative effectiveness and safety of analgesics for osteoarthritis concluded that each of the analgesics was associated with a unique set of benefits and risks, and no currently available analgesic was identified as offering a clear overall advantage compared with the others. (Chou, 2006) There are multiple medication choices listed separately (not all recommended). See Anticonvulsants for chronic pain; Antidepressants for chronic pain; Anti-epilepsy drugs (AEDs); Anti-Inflammatories; Benzodiazepines; Boswellia Serrata Resin (Frankincense); Buprenorphine; Cannabinoids; Capsaicin; Cod liver oil; Curcumin (Turmeric); Cyclobenzaprine (Flexeril®); Duloxetine (Cymbalta®); Gabapentin (Neurontin®); Glucosamine (and Chondroitin Sulfate);

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Green tea; Herbal medicines; Implantable drug-delivery systems (IDDSs); Injection with anaesthetics and/or steroids; Intrathecal drug delivery systems, medications; Intravenous regional sympathetic blocks (for RSD, nerve blocks); Ketamine; Methadone; Milnacipran (Ixel®); Muscle relaxants; Nonprescription medications; NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; Opioids (with links to multiple topics on opioids); Pycnogenol (maritime pine bark); Salicylate topicals; Topical analgesics; Topical analgesics, Compounded; Uncaria Tomentosa (Cat's Claw); Venlafaxine (Effexor®); White willow bark; & Ziconotide (Prialt®).

## **Meloxicam (Mobic®)**

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) for the relief of the signs and symptoms of osteoarthritis. See NSAIDs.

## **Meperidine (Demerol®)**

Not recommended for chronic pain control. (Lexi-Comp, 2008) Meperidine is a narcotic analgesic, similar to morphine, and has been used to relieve moderate to severe pain.

## **Metaxalone (Skelaxin®)**

Recommended with caution as a second-line option for short-term pain relief in patients with chronic LBP. Metaxalone (marketed by King Pharmaceuticals under the brand name Skelaxin®) is a muscle relaxant that is reported to be relatively non-sedating. See Muscle relaxants for more information and references.

## **Methadone**

Recommended as a second-line drug for moderate to severe pain if the potential benefit outweighs the risk. The FDA reports that they have received reports of severe morbidity and mortality with this medication. This appears, in part, secondary to the long half-life of the drug (8-59 hours). Pain relief on the other hand only lasts from 4-8 hours. Methadone should only be prescribed by providers experienced in using it. (Clinical Pharmacology, 2008)

*Pharmacokinetics:* Genetic differences appear to influence how an individual will respond to this medication. Following oral administration, significantly different blood concentrations may be obtained. Vigilance is suggested in treatment initiation, conversion from another opioid to methadone, and when titrating the methadone dose. (Weschules 2008) (Fredheim 2008)

*Adverse effects:* Delayed adverse effects may occur due to methadone accumulation during chronic administration. Systemic toxicity is more likely to occur in patients previously exposed to high doses of opioids. This may be related to tolerance that develops related to the N-methyl-D-aspartate (NMDA) receptor antagonist. Patients may respond to lower doses of methadone than would be expected based on this antagonism. One severe side effect is respiratory depression (which persists longer than the analgesic effect). Methadone should be given with caution to patients with decreased respiratory reserve (asthma, COPD, sleep apnea, severe obesity). QT prolongation with resultant serious arrhythmia has also been noted. Use methadone carefully in patients with cardiac hypertrophy and in patients at risk for hypokalemia

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(including those patients on diuretics). Methadone does have the potential for abuse. Precautions are necessary as well for employees in safety sensitive positions, including operation of a motor vehicle.

## **Steps for prescribing methadone:**

### (1) *Basic rules*

- Weigh the risks and benefits before prescribing methadone.
- Avoid prescribing 40 mg Methadone tablets for chronic non-malignant pain. This product is only FDA-approved for detoxification and maintenance of narcotic addiction.
- Closely monitor patients who receive methadone, especially during treatment initiation and dose adjustments.

### (2) *Know the information that is vital to give the patient:*

- Don't be tempted to take more methadone than prescribed if you are not getting pain relief. This can lead to a dangerous build-up that can cause death.
- All changes in methadone dose should be made by your treating practitioner.
- Methadone can make your breath slow down, or actually stop.
- Methadone can slow down your heartbeat and you might not be able to detect this.
- If you feel like you are having an irregular heartbeat, dizziness, light-headedness or fainting, call your doctor or clinic immediately. (FDA, 2006)

### (3) *Be familiar with the current SAMHSA health advisory on methadone* - The medication has become more accessible to unauthorized users.

- It can accumulate in potentially harmful doses (especially during the first few days of treatment).
- There has been a rise in Methadone-associated mortality. (SAMHSA, 2004)

### (4) *Be familiar with the FDA final policy statement on Methadone that explicitly discusses the topic, "Can Methadone be used for pain control?"*

No separate registration is required to prescribe methadone for treatment of pain. (DEA, 2006)

### (5) *Read the new prescribing information for Methadone and the new patient information section.* (Roxane, 2006)

(6) Multiple potential drug-drug interactions can occur with the use of Methadone. A complete list of medications should be obtained prior to prescribing methadone to avoid adverse events, and the patient should be warned to inform any other treating physician that they are taking this medication prior to starting and/or discontinuing medications.

## **Microcurrent electrical stimulation (MENS devices)**

See Transcutaneous electrotherapy.

## **Milnacipran (Ixel®)**

Not Recommended as it is not FDA approved and not available in the US at this time. Under study as a treatment for fibromyalgia syndrome. An FDA Phase III study demonstrated "significant therapeutic effects" of milnacipran for treatment of fibromyalgia syndrome. Milnacipran (San Diego's Cypress Bioscience Inc.) has been approved for the treatment of depression outside of the U.S. and is in a new class of antidepressants known as Norepinephrine Serotonin Reuptake Inhibitors (or NSRIs). What makes Milnacipran different from the Selective Serotonin Reuptake Inhibitors (SSRIs) – drugs like Prozac® – and Selective Norepinephrine

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Reuptake Inhibitors (SNRIs) – drugs like Effexor® – is that Milnacipran affects two neurotransmitters, norepinephrine and serotonin. (Rooks, 2007)

## **Mobic® (meloxicam)**

Mobic is a brand name for meloxicam supplied by Boehringer Ingelheim Pharmaceuticals, Inc. See Meloxicam (Mobic®).

## **Morphine**

See Opioids.

## **Morphine pumps**

See Implantable pumps for narcotics.

## **MSM (methylsulfonylmethane)**

See CRPS, medications, DMSO.

## **Multidisciplinary pain programs**

See Chronic pain programs.

## **Muscle relaxants (for pain)**

Recommend non-sedating muscle relaxants with caution as a second-line option for short-term treatment of acute exacerbations in patients with chronic LBP. (Chou, 2007) (Mens, 2005) (Van Tulder, 1998) (van Tulder, 2003) (van Tulder, 2006) (Schnitzer, 2004) (See, 2008) Muscle relaxants may be effective in reducing pain and muscle tension, and increasing mobility. However, in most LBP cases, they show no benefit beyond NSAIDs in pain and overall improvement. Also there is no additional benefit shown in combination with NSAIDs. Efficacy appears to diminish over time, and prolonged use of some medications in this class may lead to dependence. (Homik, 2004) Sedation is the most commonly reported adverse effect of muscle relaxant medications. These drugs should be used with caution in patients driving motor vehicles or operating heavy machinery. Drugs with the most limited published evidence in terms of clinical effectiveness include chlorzoxazone, methocarbamol, dantrolene and baclofen. (Chou, 2004) According to a recent review in *American Family Physician*, skeletal muscle relaxants are the most widely prescribed drug class for musculoskeletal conditions (18.5% of prescriptions), and the most commonly prescribed antispasmodic agents are carisoprodol, cyclobenzaprine, metaxalone, and methocarbamol, but despite their popularity, skeletal muscle relaxants should not be the primary drug class of choice for musculoskeletal conditions. (See2, 2008)

*Classifications:* Muscle relaxants are a broad range of medications that are generally divided into antispasmodics, antispasticity drugs, and drugs with both actions. (See, 2008) (van Tulder, 2006)

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**ANTISPASTICITY DRUGS:** Used to decrease spasticity in conditions such as cerebral palsy, MS, and spinal cord injuries (upper motor neuron syndromes). Associated symptoms include exaggerated reflexes, autonomic hyperreflexia, dystonia, contractures, paresis, lack of dexterity and fatigability. (Chou, 2004)

**Baclofen (Lioresal®, generic available):** The mechanism of action is blockade of the pre- and post-synaptic GABA<sub>B</sub> receptors. It is recommended orally for the treatment of spasticity and muscle spasm related to multiple sclerosis and spinal cord injuries. Baclofen has been noted to have benefits for treating lancinating, paroxysmal neuropathic pain (trigeminal neuralgia, non-FDA approved). (ICSI, 2007)

*Side Effects:* Sedation, dizziness, weakness, hypotension, nausea, respiratory depression and constipation. This drug should not be discontinued abruptly (withdrawal includes the risk of hallucinations and seizures). Use with caution in patients with renal and liver impairment.

*Dosing:* Oral: 5 mg three times a day. Upward titration can be made every 3 days up to a maximum dose of 80 mg a day. (See, 2008)

**Dantrolene (Dantrium®, generic available):** Not recommended. The mechanism of action is a direct inhibition of muscle contraction by decreasing the release of calcium from the sarcoplasmic reticulum.

*Side Effects:* A black-box warning has been issued about symptomatic fatal or nonfatal hepatitis.

*Dosing:* 25 mg a day for 7 days, 25 mg three times a day for 7 days, 50 mg three times a day for 7 days and then 100 mg three times a day. (See, 2008)

**ANTISPASMODICS:** Used to decrease muscle spasm in conditions such as LBP although it appears that these medications are often used for the treatment of musculoskeletal conditions whether spasm is present or not. The mechanism of action for most of these agents is not known. (Chou, 2004)

**Cyclobenzaprine (Flexeril®, Amrix®, Fexmid™, generic available):** Recommended for a short course of therapy. Limited, mixed-evidence does not allow for a recommendation for chronic use. Cyclobenzaprine is a skeletal muscle relaxant and a central nervous system depressant with similar effects to tricyclic antidepressants (e.g. amitriptyline). Cyclobenzaprine is more effective than placebo in the management of back pain, although the effect is modest and comes at the price of adverse effects. It has a central mechanism of action, but it is not effective in treating spasticity from cerebral palsy or spinal cord disease. Cyclobenzaprine is associated with a number needed to treat of 3 at 2 weeks for symptom improvement. The greatest effect appears to be in the first 4 days of treatment. (Browning, 2001) (Kinkade, 2007) (Toth, 2004) See Cyclobenzaprine. Cyclobenzaprine has been shown to produce a modest benefit in treatment of fibromyalgia. Cyclobenzaprine-treated patients with fibromyalgia were 3 times more likely to report overall improvement and to report moderate reductions in individual symptoms (particularly sleep). A meta-analysis concluded that the number needed to treat for patients with fibromyalgia was 4.8. (ICSI, 2007) (Tofferi, 2004)

*Side Effects:* Include anticholinergic effects (drowsiness, urinary retention and dry mouth). Sedative effects may limit use. Headache has been noted. This medication should be avoided in patients with arrhythmias, heart block, heart failure and recent myocardial infarction. Side effects limit use in the elderly. (See, 2008) (Toth, 2004)

*Dosing:* 5 mg three times a day. Can be increased to 10 mg three times a day. This medication is not recommended to be used for longer than 2-3 weeks. (See, 2008)

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**Methocarbamol (Robaxin®, Relaxin™, generic available):** The mechanism of action is unknown, but appears to be related to central nervous system depressant effects with related sedative properties. This drug was approved by the FDA in 1957.

*Side Effects:* Drowsiness, dizziness and lightheadedness.

*Dosing:* 1500 mg four times a day for the first 2-3 days, then decreased to 750 mg four times a day. (See, 2008)

**Metaxalone (Skelaxin®, generic available)** is reported to be a relatively non-sedating muscle relaxant. The exact mechanism of action is unknown, but the effect is presumed to be due to general depression of the central nervous system. Metaxalone was approved by the FDA in 1964 and data to support approval were published in the mid-1960s. (Toth, 2004)

*Side Effects:* Dizziness and drowsiness, although less than that compared to other skeletal muscle relaxants. Other side effects include headache, nervousness, nausea, vomiting, and GI upset. A hypersensitivity reaction (rash) has been reported. Use with caution in patients with renal and/or hepatic failure.

*Dosing:* 800 mg three to four times a day (See, 2008)

**Chlorzoxazone (Parafon Forte®, Paraflex®, Relax™DMS, Remular S™, generic available):** this drug works primarily in the spinal cord and the subcortical areas of the brain. The mechanism of action is unknown but the effect is thought to be due to general depression of the central nervous system. Advantages over other muscle relaxants include reduced sedation and less evidence for abuse. (See, 2008)

*Side Effects:* Drowsiness and dizziness. Urine discoloration may occur. Avoid use in patients with hepatic impairment.

*Dosing:* 250-750 mg three times a day to four times a day.

**Carisoprodol (Soma®, Soprodal 350™, Vanadom®, generic available):** Neither of these formulations is recommended for longer than a 2 to 3 week period. Carisoprodol is metabolized to meprobamate an anxiolytic that is a schedule IV controlled substance. Carisoprodol is classified as a schedule IV drug in several states but not on a federal level. It is suggested that its main effect is due to generalized sedation as well as treatment of anxiety. This drug was approved for marketing before the FDA required clinical studies to prove safety and efficacy. Withdrawal symptoms may occur with abrupt discontinuation. (See, 2008) (Reeves, 2003) For more details, see Carisoprodol, where it is “Not recommended.” See also Weaning of medications.

*Side Effects:* drowsiness, psychological and physical dependence, & withdrawal with acute discontinuation.

*Dosing:* 250 mg-350 mg four times a day. (See, 2008)

**Orphenadrine (Norflex®, Banflex®, Antiflex™, Mio-Rel™, Orphenate™, generic available):** This drug is similar to diphenhydramine, but has greater anticholinergic effects. The mode of action is not clearly understood. Effects are thought to be secondary to analgesic and anticholinergic properties. This drug was approved by the FDA in 1959.

*Side Effects:* Anticholinergic effects (drowsiness, urinary retention, dry mouth). Side effects may limit use in the elderly. This medication has been reported in case studies to be abused for euphoria and to have mood elevating effects. (Shariatmadari, 1975)

*Dosing:* 100 mg twice a day; combination products are given three to four times a day. (See, 2008)

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## **ANTISPASTICITY/ANTISPASMODIC DRUGS:**

**Tizanidine (Zanaflex®, generic available)** is a centrally acting alpha2-adrenergic agonist that is FDA approved for management of spasticity; unlabeled use for low back pain. (Malanga, 2008) Eight studies have demonstrated efficacy for low back pain. (Chou, 2007) One study (conducted only in females) demonstrated a significant decrease in pain associated with chronic myofascial pain syndrome and the authors recommended its use as a first line option to treat myofascial pain. (Malanga, 2002) May also provide benefit as an adjunct treatment for fibromyalgia. (ICSI, 2007)

Side effects: somnolence, dizziness, dry mouth, hypotension, weakness, hepatotoxicity (LFTs should be monitored baseline, 1, 3, and 6 months). (See, 2008)

Dosing: 4 mg initial dose; titrate gradually by 2 – 4 mg every 6 – 8 hours until therapeutic effect with tolerable side-effects; maximum 36 mg per day. (See, 2008) Use with caution in renal impairment; should be avoided in hepatic impairment. Tizanidine use has been associated with hepatic aminotransaminase elevations that are usually asymptomatic and reversible with discontinuation.

**Benzodiazepines:** Not recommended due to rapid development of tolerance and dependence. There appears to be little benefit for the use of this class of drugs over nonbenzodiazepines for the treatment of spasm. (See, 2008) See Benzodiazepines.

## **Myotherapy**

See Massage therapy.

## **Nabilone**

Recommended for treatment of chemotherapy-induced nausea, but not recommended for pain until there is better evidence. In a preliminary, placebo-controlled, 1-month trial, the marijuana-based synthetic drug nabilone (Cesamet, Valeant Pharmaceuticals) showed promise for temporary pain relief for fibromyalgia patients. Future studies with a longer duration of treatment and a stable dose are still needed. When interpreting the study results, it is important to note that the study drug was costly, the study was done in a small number of patients, and there was a high dropout rate. In addition, the dropout patients were not included in an intention-to-treat analysis, which would have resulted in a lower improvement rate. (Skrabek, 2008) Nabilone was approved in 1985 by the FDA for treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemetics. See also Cannabinoids.

## **Naproxen**

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) for the relief of the signs and symptoms of osteoarthritis. See NSAIDs. See Anti-inflammatory medications.

## **Narcotics**

See Opioids.

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## **Nerve blocks**

See Intravenous regional sympathetic blocks (for RSD, nerve blocks).

## **Neuromodulation devices**

See Spinal cord stimulators.

## **Neuromuscular electrical stimulation (NMES devices)**

See Transcutaneous electrotherapy.

## **Neurontin® (gabapentin)**

Neurontin® is a brand name for gabapentin produced by Pfizer subsidiary Parke-Davis. See Gabapentin.

## **Nonprescription medications**

Recommended. Acetaminophen (safest); NSAIDs (aspirin, ibuprofen). (Bigos, 1999) There should be caution about daily doses of acetaminophen and liver disease if over 4 g/day or in combination with other NSAIDs. (Watkins, 2006) See also NSAIDs (non-steroidal anti-inflammatory drugs).

## **Norepinephrine serotonin reuptake inhibitors (NSRIs)**

See Duloxetine (Cymbalta®); & Milnacipran (Ixel®).

## **NSAIDs (non-steroidal anti-inflammatory drugs)**

Specific recommendations:

*Osteoarthritis (including knee and hip):* Recommended at the lowest dose for the shortest period in patients with moderate to severe pain. Acetaminophen may be considered for initial therapy for patients with mild to moderate pain, and in particular, for those with gastrointestinal, cardiovascular or renovascular risk factors. NSAIDs appear to be superior to acetaminophen, particularly for patients with moderate to severe pain. There is no evidence to recommend one drug in this class over another based on efficacy. In particular, there appears to be no difference between traditional NSAIDs and COX-2 NSAIDs in terms of pain relief. The main concern of selection is based on adverse effects. COX-2 NSAIDs have fewer GI side effects at the risk of increased cardiovascular side effects, although the FDA has concluded that long-term clinical trials are best interpreted to suggest that cardiovascular risk occurs with all NSAIDs and is a class effect (with naproxyn being the safest drug). There is no evidence of long-term effectiveness for pain or function. (Chen, 2008) (Laine, 2008)

*Back Pain - Acute exacerbations of chronic pain:* Recommended as a second-line treatment after acetaminophen. In general, there is conflicting evidence that NSAIDs are more effective than acetaminophen for acute LBP. (van Tulder, 2006) (Hancock, 2007) For patients with acute low

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back pain with sciatica a recent Cochrane review (including three heterogeneous randomized controlled trials) found no differences in treatment with NSAIDs vs. placebo. In patients with axial low back pain this same review found that NSAIDs were not more effective than acetaminophen for acute low-back pain, and that acetaminophen had fewer side effects. (Roelofs-Cochrane, 2008) The addition of NSAIDs or spinal manipulative therapy does not appear to increase recovery in patients with acute low back pain over that received with acetaminophen treatment and advice from their physician. (Hancock, 2007)

*Back Pain - Chronic low back pain:* Recommended as an option for short-term symptomatic relief. A Cochrane review of the literature on drug relief for low back pain (LBP) suggested that NSAIDs were no more effective than other drugs such as acetaminophen, narcotic analgesics, and muscle relaxants. The review also found that NSAIDs had more adverse effects than placebo and acetaminophen but fewer effects than muscle relaxants and narcotic analgesics. In addition, evidence from the review suggested that no one NSAID, including COX-2 inhibitors, was clearly more effective than another. (Roelofs-Cochrane, 2008) See also Anti-inflammatory medications.

*Neuropathic pain:* There is inconsistent evidence for the use of these medications to treat long-term neuropathic pain, but they may be useful to treat breakthrough and mixed pain conditions such as osteoarthritis (and other nociceptive pain) in with neuropathic pain. (Namaka, 2004) (Gore, 2006) See NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function. Besides the above well-documented side effects of NSAIDs, there are other less well-known effects of NSAIDs, and the use of NSAIDs has been shown to possibly delay and hamper healing in all the soft tissues, including muscles, ligaments, tendons, and cartilage. (Maroon, 2006)

### NSAIDs, GI symptoms & cardiovascular risk

Recommend with precautions as indicated below.

*Clinicians should weight the indications for NSAIDs against both GI and cardiovascular risk factors.*

*Determine if the patient is at risk for gastrointestinal events:* (1) age > 65 years; (2) history of peptic ulcer, GI bleeding or perforation; (3) concurrent use of ASA, corticosteroids, and/or an anticoagulant; or (4) high dose/multiple NSAID (e.g., NSAID + low-dose ASA). Recent studies tend to show that *H. Pylori* does not act synergistically with NSAIDS to develop gastroduodenal lesions.

#### Recommendations

*Patients with no risk factor and no cardiovascular disease:* Non-selective NSAIDs OK (e.g, ibuprofen, naproxen, etc.)

*Patients at intermediate risk for gastrointestinal events and no cardiovascular disease:*(1) A non-selective NSAID with either a PPI (Proton Pump Inhibitor, for example, 20 mg omeprazole daily) or misoprostol (200 µg four times daily) or (2) a Cox-2 selective agent. Long-term PPI use (> 1 year) has been shown to increase the risk of hip fracture (adjusted odds ratio 1.44).

*Patients at high risk for gastrointestinal events with no cardiovascular disease:* A Cox-2 selective agent plus a PPI if absolutely necessary.

*Patients at high risk of gastrointestinal events with cardiovascular disease:* If GI risk is high the suggestion is for a low-dose Cox-2 plus low dose Aspirin (for cardioprotection) and a PPI. If cardiovascular risk is greater than GI risk the suggestion is naproxyn plus low-dose aspirin plus a

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PPI. (Laine, 2006) (Scholmerich, 2006) (Nielsen, 2006) (Chan, 2004) (Gold, 2007) (Laine, 2007)

Cardiovascular disease: A non-pharmacological choice should be the first option in patients with cardiac risk factors. It is then suggested that acetaminophen or aspirin be used for short-term needs. An opioid also remains a short-term alternative for analgesia.

*Major risk factors (recent MI, or coronary artery surgery, including recent stent placement):* If NSAID therapy is necessary, the suggested treatment is naproxyn plus low-dose aspirin plus a PPI.

*Mild to moderate risk factors:* If long-term or high-dose therapy is required, full-dose naproxen (500 mg twice a day) appears to be the preferred choice of NSAID. If naproxyn is ineffective, the suggested treatment is (1) the addition of aspirin to naproxyn plus a PPI, or (2) a low-dose Cox-2 plus ASA. Cardiovascular risk does appear to extend to all non-aspirin NSAIDs, with the highest risk found for the Cox-2 agents. (Johnsen, 2005) (Lanas, 2006) (Antman, 2007) (Laine, 2007)

Use with Aspirin for cardioprotective effect:

*In terms of GI protective effect:* The GI protective effect of Cox-2 agents is diminished in patients taking low-dose aspirin and a PPI may be required for those patients with GI risk factors. (Laine, 2007)

*In terms of the actual cardioprotective effect of aspirin:* Traditional NSAIDs (both ibuprofen and naproxen) appear to attenuate the antiplatelet effect of enteric-coated aspirin and should be taken 30 minutes after ASA or 8 hours before. (Antman, 2007) Cox-2 NSAIDs and diclofenac (a traditional NSAID) do not decrease anti-platelet effect. (Laine, 2007)

Use of NSAIDs and SSRIs: The concurrent use of SSRIs and NSAIDs is associated with moderate excess relative risk of serious upper GI events when compared to NSAIDs alone. This risk was higher for non-selective NSAIDs when compared to Cox-2 selective agents (adjusted odds ratio of 1.77 and 1.33, respectively). (Helin-Salmivaara, 2007)

*Treatment of dyspepsia secondary to NSAID therapy:* Stop the NSAID, switch to a different NSAID, or consider H2-receptor antagonists or a PPI.

### NSAIDs, hypertension and renal function

Recommend with precautions as indicated below.

NSAIDs can increase blood pressure by an average of 5 to 6 mm in patients with hypertension. They may cause fluid retention, edema, and rarely, congestive heart failure. (Sustained blood pressure elevation in the elderly is associated with increases in hemorrhagic stroke, congestive heart failure and ischemic cardiac events.) The risk appears to be higher in patients with congestive heart failure, kidney disease or liver disease.

*Normotensive patients:* NSAIDs appear to have minimal effect on blood pressure in normotensive patients. (Laine, 2007)

*Hypertensive patients:* All NSAIDs have the potential to raise blood pressure in susceptible patients. The greatest risk appears to occur in patients taking the following anti-hypertensive therapy: angiotensin-converting enzyme (ACE) inhibitors; angiotensin receptor blockers; beta-blockers; or diuretics. In addition congestive heart failure may develop due to fluid retention.

*Patients with mild to moderate renal dysfunction:* All NSAIDs are relatively contraindicated in patients with renal insufficiency, congestive heart failure, or volume excess (such as cirrhosis). Oral opioids are an option for treatment.

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*Treatment recommendations:* Blood pressure should be measured as well as evidence of fluid excess in normotensive patients within 2-4 weeks of beginning treatment and on each visit.

## NSAIDs, specific drug list & adverse effects

Recommended with cautions below. Disease-State Warnings for all NSAIDs: All NSAIDs have [U.S. **Boxed Warning**]: for associated risk of adverse cardiovascular events, including, MI, stroke, and new onset or worsening of pre-existing hypertension. NSAIDs should never be used right before or after a heart surgery (CABG - coronary artery bypass graft). NSAIDs can cause ulcers and bleeding in the stomach and intestines at any time during treatment (FDA Medication Guide). See NSAIDs, GI Symptoms and Cardiovascular Risks. *Other disease-related concerns (non-boxed warnings):* *Hepatic:* Use with caution in patients with moderate hepatic impairment and not recommended for patients with severe hepatic impairment. Borderline elevations of one or more liver enzymes may occur in up to 15% of patients taking NSAIDs. *Renal:* Use of NSAIDs may compromise renal function. FDA Medication Guide is provided by FDA mandate on all prescriptions dispensed for NSAIDs. *Routine Suggested Monitoring:* Package inserts for NSAIDs recommend periodic lab monitoring of a CBC and chemistry profile (including liver and renal function tests). There has been a recommendation to measure liver transaminases within 4 to 8 weeks after starting therapy, but the interval of repeating lab tests after this treatment duration has not been established. Routine blood pressure monitoring is recommended. *Overall Dosing Recommendation:* It is generally recommended that the lowest effective dose be used for all NSAIDs for the shortest duration of time consistent with the individual patient treatment goals. Specific NSAID Classes are outlined below:

**Selective COX-2 NSAIDs:** Celecoxib (Celebrex®) is the only available COX-2 in the United States. No generic is available. *Mechanism of Action:* Inhibits prostaglandin synthesis by decreasing cyclooxygenase-2 (COX-2). At therapeutic concentrations, cyclooxygenase-1 (COX-1) is not inhibited. In animal models it works as an anti-inflammatory, analgesic, and antipyretic. It does not have an anti-platelet effect and is not a substitute for aspirin for cardiac prophylaxis. *Use:* Relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, [and] ankylosing spondylitis. *Side Effects:* See NSAIDs, hypertension and renal function; & NSAIDs, GI Symptoms and Cardiovascular Risks. *Cardiovascular:* Hypertension ( $\leq 13\%$ ) *CNS:* headache (15.8%), dizziness (1% - 2%), insomnia (2.3%); *GI:* diarrhea (4% to 11%), dyspepsia (8.8% vs. 12.8% for ibuprofen and 6.2% for placebo), diarrhea (5.6%), abdominal pain (4.1% vs. 9% for ibuprofen and 2.8% for placebo), N/V (3.5%), gastroesophageal reflux ( $\leq 5\%$ ), flatulence (2.2%); *Neuromuscular/ skeletal:* arthralgia (7%), back pain (3%); *Respiratory:* upper respiratory tract infection (8%), cough (7%), sinusitis (5%), rhinitis (2%), pharyngitis (2%); *Skin Rash* (2%) – discontinue if rash develops; *Peripheral Edema* (2.1%). *Recommended Dose:* 200 mg a day (single dose or 100 mg twice a day). (Celebrex® package insert)

**Combination (NSAID/GI protectant):** Arthrotec® (diclofenac/ misoprostol) 50mg/200mcg, 75mg/20mcg. [**Black Box Warning**]: Do not administer Arthrotec®/misoprostol to pregnant women because it can cause abortion. *Mechanism of action:* Combines a diclofenac (an NSAID) with misoprostol, an agent that inhibits basal and nocturnal gastric acid secretion and has some mucosal protective properties. Misoprostol is available as Cytotec®. *Uses:* Indicated for the treatment of the signs and symptoms of osteoarthritis in patients at high risk for developing

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NSAID-induced gastric or duodenal ulcers and their complications. These two products are available as separate medications if you need to individualize therapy. *Side Effects:* See diclofenac. *Misoprostol side effects:* (vs. diclofenac alone). The following symptoms were increased over and above that found for diclofenac alone with the addition of misoprostol: Abdominal pain (21% with Arthrotec and 15% with diclofenac); Diarrhea (19% with Arthrotec vs. 11% with diclofenac); Dyspepsia (14% for Arthrotec vs. 11% for diclofenac); Nausea/vomiting (11% for Arthrotec vs. 6% for diclofenac); Flatulence (9% for Arthrotec vs. 4% for diclofenac). Diarrhea and abdominal pain usually resolve in 2 to 7 days. *Dosing:* The recommended dose for OA is diclofenac 50mg/misoprostol 200mcg t.i.d. In patients that may not tolerate this dose, 50mg/200mcg b.i.d and 75mg/200mcg b.i.d. may be prescribed, but are somewhat less effective in ulcer prevention. (Arthrotec® Package Insert) (Bocanegra, 1998)

**NONSELECTIVE NSAIDS:** (Inhibits COX-1 and COX-2) Mechanism of action: Inhibits prostaglandin synthesis by decreasing the activity of the enzymes COX-1 and COX-2, which results in decreased formation of prostaglandins involved in the physiologic response of pain and inflammation. Side Effects: See Disease-state warnings above. Other common side effects include the following. CNS: headache, dizziness, insomnia; Skin: rash including life-threatening skin reactions (Stevens-Johnson syndrome) **\*\*Discontinue if rash develops\*\***; GI: abdominal cramps, nausea/vomiting, diarrhea, constipation, flatulence; Otic: Tinnitus; Hematologic: Anemia. Specific NSAIDS are listed below:

*Diclofenac Sodium (Voltaren®, Voltaren-XR®) generic available:* (Voltaren®, diclofenac sodium enteric-coated tablet Package Insert), (Voltaren®-XR, diclofenac sodium extended-release tablets Package Insert)

*Diclofenac Potassium (Cataflam®, generic available):* (Cataflam®, diclofenac potassium immediate-release tablets Package Insert) Different formulations of diclofenac are not necessarily bioequivalent. *Dosing:* Cataflam®: *Osteoarthritis: Adults:* 50 mg PO 2—3 times daily. Dosages > 150 mg/day PO are not recommended. *Pain:* 50mg PO 3 times per day (max dose is 150mg/day). An initial dose of 100 mg PO followed by 50-mg doses may provide better relief. Voltaren®: *Osteoarthritis:* 50 mg PO 2—3 times daily or 75 mg PO twice daily. Dosages > 150 mg/day PO are not recommended. *Ankylosing spondylitis:* 25 mg PO 4 times a day with an extra 25-mg dose at bedtime if necessary. Voltaren®-XR: 100 mg PO once daily for chronic therapy. Voltaren®-XR should only be used as chronic maintenance therapy.

*Diflunisal (Dolobid®, generic available): Dosing: Mild to moderate pain* (arthralgia, bone pain, myalgia); 1 gm initially, followed by 500mg every 12 hours; some patients may require 500mg PO every 8 hours (Max 1500mg/day). *Osteoarthritis:* 250-500mg PO twice daily (Max 1500mg/day). (Dolubid® Package Insert)

*Etodolac (Lodine®, Lodine XL®, generic available): Dosing: Lodine®: Osteoarthritis:* 300mg PO 2-3 times daily or 400 – 500mg twice daily (doses > 1000mg/day have not been evaluated). Lodine®-XL: *Osteoarthritis:* 400 to 1000 mg once daily. A therapeutic response may not be seen for 1-2 weeks.

*Fenoprofen (Nalfon®, generic available):* 200, 600 mg. *Dosing: osteoarthritis;* (off-label use for ankylosing spondylitis); 300 – 600mg PO 3 to 4 times per day (Max daily dose is 3200mg). Improvement may take as long as 2 to 3 weeks. *Mild to moderate pain* (off-label use for bone pain): 200mg PO every 4 to 6 hours as needed.

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*Flurbiprofen (Ansaid®, generic available):* 50, 100 mg. *Dosing: Osteoarthritis and mild to moderate pain:* 200-300mg per day at intervals of 2 to 4 divided doses. The maximum daily dose is 300 mg/day and the maximum divided dose is 100 mg (for instance, 100 mg twice a day).

*Ibuprofen (Motrin®, Advil® [otc], generic available):* 300, 400, 600, 800 mg. *Dosing: Osteoarthritis and off-label for ankylosing spondylitis:* 1200 mg to 3200 mg daily. Individual patients may show no better response to 3200 mg as 2400 mg, and sufficient clinical improvement should be observed to offset potential risk of treatment with the increased dose. Higher doses are generally recommended for rheumatoid arthritis: 400-800 mg PO 3-4 times a day, use the lowest effective dose. Higher doses are usually necessary for osteoarthritis. Doses should not exceed 3200 mg/day. *Mild pain to moderate pain:* 400 mg PO every 4-6 hours as needed. Doses greater than 400 mg have not provided greater relief of pain.

*Indomethacin (Indocin®, Indocin SR®, generic available):* This medication is generally not recommended in the elderly due to increased risk of adverse effects. *Dosing: Osteoarthritis, or ankylosing spondylitis:* NOTE: If minor adverse effects develop as the dosage is increased, rapidly reduce the dose to a tolerated dose and closely observe the patient. If severe adverse reactions occur, discontinue. *Regular-release capsules, suspension (25 mg and 50 mg):* 25 mg PO 2—3 times a day with food or antacids; may increase dose by 25 mg/day PO every 7 days up to 150—200 mg/day. In patients who have persistent night pain and/or morning stiffness, administer a large portion of the total daily dose, up to 100 mg/dose, at bedtime. *Sustained-release capsules (75 mg):* Initially, 75 mg PO daily. Use the regular-release capsules to provide a higher dose, if needed. If 150 mg daily is tolerated and is needed, a 75 mg sustained-release capsule PO bid may be used. After the acute phase is under control, attempt to decrease the dosage to the lowest effective dosage or discontinue the drug. *Moderate pain to severe pain including painful shoulder (bursitis and tendinitis) as well as off-label for bone pain: Regular-release capsules, suspension (25 mg and 50 mg):* 75-150 mg/day PO in 3-4 divided doses. Discontinue the drug once the signs and symptoms of the inflammation have been controlled for several days. The usual length of therapy is 7-14 days. *Sustained-release capsules (75 mg):* 75 mg PO 1—2 times per day.

*Ketoprofen 50, 75 mg, Ketoprofen ER 200 mg: Dosing: Osteoarthritis:* Regular release capsule 50mg four times per day or 75mg three times per day (max 300mg/day). XR capsule 200mg once daily. *Mild to moderate pain:* Regular release capsule 50mg every 6 to 8 hours (Max 300mg/day);

*Ketorolac (Toradol®, generic available):* 10 mg. **[Boxed Warning]:** This medication is not indicated for minor or chronic painful conditions.

*Mefenamic Acid (Ponstel®, generic available):* 250 mg. *Mild and moderate pain:* Initially, 500 mg PO followed by 250 mg every 6 hours as needed for no longer than 7 days. (Ponstel® Package Insert)

*Meloxicam (Mobic®, generic available):* 7.5, 15 mg. *Dosing: Osteoarthritis:* The usual initial dose is 7.5 mg/day, although some patients may receive additional benefit with an increase to 15 mg a day. The maximum dose is 15 mg/day. *Use for mild to moderate pain is off-label.* (Mobic® Package Insert)

*Nabumetone (Relafen®, generic available):* 500, 750 mg. *Dosing: Osteoarthritis:* The recommended starting dose is 1000 mg PO. The dose can be divided into 500 mg PO twice a day. Additional relief may be obtained with a dose of 1500 mg to 2000 mg per day. The maximum dose is 2000 mg/day. Patients weighing less than 50 kg may be less likely to require

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doses greater than 1000 mg/day. The lowest effective dose of nabumetone should be sought for each patient. *Use for moderate pain is off-label.* (Relafen® Package Insert)

*Naproxen (Naprosyn®):* delayed release (EC-Naprosyn®), as Sodium salt (Anaprox®, Anaprox DS®, Aleve® [otc]) Generic available; extended-release (Napreelan®): 375 mg. Different dose strengths and formulations of the drug are not necessarily bioequivalent. *Dosing Information: Osteoarthritis or ankylosing spondylitis:* Dividing the daily dose into 3 doses versus 2 doses for immediate-release and delayed-release formulations generally does not affect response. Morning and evening doses do not have to be equal in size. The dose may be increased to 1500 mg/day of naproxyn for limited periods when a higher level of analgesic/anti-inflammatory activity is required (for up to 6 months). *Naprosyn® or naproxyn:* 250-500 mg PO twice daily. *Anaprox:* 275-550 mg PO twice daily. (total dose may be increased to 1650 mg a day for limited periods). *EC-Naprosyn:* 375 mg or 500 mg twice daily. The tablet should not be broken, crushed or chewed to maintain integrity of the enteric coating. *Napreelan®:* Two 375 mg tablets (750 mg) PO once daily or two 500 mg tablets (1000 mg) once daily. If required (and a lower dose was tolerated) Napreelan® can be increased to 1500 mg once daily for limited periods (when higher analgesia is required). *Pain: Naprosyn® or naproxyn:* 250-500 mg PO twice daily. The maximum dose on day one should not exceed 1250 mg and 1000 mg on subsequent days. *Anaprox:* 275-550 mg PO twice daily. The maximum dose on day one should not exceed 1375 mg and 1100 mg on subsequent days. *Extended-release Napreelan®:* Not recommended due to delay in absorption. (Napreelan® Package Insert)

*Oxaprozin (Daypro®, generic available):* 600 mg. *Dosing: Osteoarthritis:* Two 600 mg caplets (1200 mg total) given PO once daily. The maximum dose is 1800 mg/day (26 mg/kg, whichever is lower). For patients with low body weight (i.e., < 50 kg or 110 pounds), an initial dosage of 600 mg PO once daily is recommended. Patients with severe renal impairment should initiate therapy at 600 mg/day. An increase to 1200 mg can be cautiously increased, but only with close monitoring. For quick onset of action, a one-time loading dose of 1200 to 1800 mg can be given (do not exceed 26 mg/kg). *Mild to moderate pain:* Used off-label. (Daypro® Package Insert)

*Piroxicam (Feldene®, generic available):* 10, 20 mg. *Dosing: Osteoarthritis:* 20 mg PO once daily. Adjust dose, as needed. The daily dose may be divided in two doses, if desired. This drug has a long half-life and steady state is not reached for 7-12 days. There is a progressive response over several weeks and therapy effect should not be assessed for two weeks after initiating therapy. *Elderly:* Initially, 10 mg PO once daily. Adjust dose, as needed, up to 20 mg/day. *Pain:* Not recommended. (Feldene Package Insert)

*Sulindac (Clinoril®, generic available):* 150, 200 mg. *Dosing Information: Osteoarthritis, ankylosing spondylitis:* Initially, 150 mg PO twice daily. Adjust dosage as needed. May increase up to 200 mg PO twice daily depending on patient response. The maximum dose is 400 mg a day. *Mild to moderate pain:* Off label. (Clinoril® Package Insert)

*Tolmetin (Tolectin®, Tolectin DS, Tolectin 600mg, generic available):* *Dosing Information: Osteoarthritis (chronic):* Initially, 400 mg PO three times a day. If needed, adjust dose upward or downward after 1-2 weeks. Maintenance dosage is usually 600-1800 mg/day PO in 3-4 divided doses. (Max dose is 1800mg/day). Symptomatic improvement may occur within 7 days, with progressive improvement during successive weeks of therapy. (Clinical Pharmacology, 2008) (Lexi-Comp, 2008)

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## Nucleoplasty

Not recommended. Given the extremely low level of evidence available for Nucleoplasty (Coblation Nucleoplasty), and the lack of clinical trials, it is recommended that this procedure be regarded as experimental at this time. (Manchikanti, 2003) (Boswell, 2007) (ArthroCare Corp, Sunnyvale, CA, introduced the Micro DisCoblator in 2003 to enable minimally invasive disc decompression. Total 2003 Revenue \$119 million. Company literature: “The Nucleoplasty procedure uses a minimally-invasive catheter to create a pathway into the disc. Radio wave signals are sent through the transmitter into the nucleus of the herniated disc. The radio waves produce a low-temperature ionized gas that breaks up molecular bonds in the spongy nucleus, removing tissue volume. The Nucleoplasty procedure uses an FDA-cleared device, and is a clinically proven treatment with over 20,000 patients treated.”)

## Occupational therapy (OT)

See Physical medicine.

## Omega-3 EFAs

See Cod liver oil.

## Opioids

This topic is covered under multiple headings. See more specific entries, as follows: Opioids, criteria for use; Opioids for chronic pain; Opioids for neuropathic pain; Opioids for osteoarthritis; Opioids, cancer pain vs. nonmalignant pain; Opioids, dealing with misuse & addiction; Opioids, differentiation: dependence & addiction; Opioids, dosing; Opioids, indicators for addiction; Opioids, long-term assessment; Opioids, pain treatment agreement; Opioids, psychological intervention; Opioids, screening for risk of addiction (tests); Opioids, state medical boards guidelines; Opioids, steps to avoid misuse/addiction; Detoxification; Substance abuse (tolerance, dependence, addiction); Weaning of medications; Implantable drug-delivery systems (IDDSs); Methadone; Rapid detox; Testosterone replacement for hypogonadism (related to opioids); Opioid hyperalgesia & Opioids, specific drug list. Opioid drugs are also referred to opiate analgesics, narcotic analgesics, or schedule C (II -IV) controlled substances. Opioid analgesics are a class of drugs (e.g., morphine, codeine, and methadone) that have a primary indication to relieve symptoms related to pain. Opioid drugs are available in various dosage forms and strengths. They are considered the most powerful class of analgesics that may be used to manage chronic pain. These medications are generally classified according to potency and duration of dosage duration.

### ***Overall Classification:***

*Pure-agonists:* include natural and synthetic opioids such as morphine sulfate (MS Contin®), hydromorphone (Dilaudid®), oxymorphone (Numorphan®), levorphanol (Levo-Dromoran®), codeine (Tylenol w/Codeine 3®), hydrocodone (Vicodin®), oxycodone (OxyContin®), methadone (Dolophine HCl®), and fentanyl (Duragesic®). This group of opioids does not have a

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

ceiling effect for their analgesic efficacy nor do they antagonize (reverse) the effects of other pure opioids. (Baumann, 2002) Morphine is the most widely used type of opioid analgesic for the treatment of moderate to severe pain due to its availability, the range of doses offered, and its low cost.

*Partial agonists-antagonists:* agents that stimulate the analgesic portion of opioid receptors while blocking or having little or no effect on toxicity. This group of opiates includes buprenorphine (Suboxone®). Partial agonists-antagonists have lower abuse potential than pure-agonists, however the side effects of this class of analgesics include hallucinations and dysphoria. *Opioid antagonists* such as naloxone are included in this class. They are most often used to reverse the effects of agonists and agonist-antagonist derived opioids. (Baumann, 2002)

*Mixed agonists-antagonists:* another type of opiate analgesics that may be used to treat pain. They include such drugs as butorphanol (Stadol®), dezocine (Dalgan®), nalbuphine (Nubain®) and pentazocine (Talwin®). (Baumann, 2002) Mixed agonists-antagonists have limited use among chronic pain patients because of their ceiling effect for analgesia that results in the analgesic effect not increasing with dose escalation.

*Central acting analgesics:* an emerging fourth class of opiate analgesic that may be used to treat chronic pain. This small class of synthetic opioids (e.g., Tramadol) exhibits opioid activity and a mechanism of action that inhibits the reuptake of serotonin and norepinephrine. Central analgesics drugs such as Tramadol (Ultram®) are reported to be effective in managing neuropathic pain. (Kumar, 2003) Side effects are similar to traditional opioids.

### ***Opioid Classifications: Short-acting/Long-acting opioids:***

*Short-acting opioids:* also known as “normal-release” or “immediate-release” opioids are seen as an effective method in controlling chronic pain. They are often used for intermittent or breakthrough pain. These agents are often combined with other analgesics such as acetaminophen and aspirin. These adjunct agents may limit the upper range of dosing of short-acting agents due to their adverse effects. The duration of action is generally 3-4 hours. Short-acting opioids include Morphine (Roxanol®), Oxycodone (OxyIR®, Oxyfast®), Endocodone®, Oxycodone with acetaminophen, (Roxilox®, Roxicet®, Percocet®, Tylox®, Endocet®), Hydrocodone with acetaminophen, (Vicodin®, Lorcet®, Lortab®, Zydone®, Hydrocet®, Norco®), Hydromorphone (Dilaudid®, Hydrostat®). (Baumann, 2002)

*Long-acting opioids:* also known as “controlled-release”, “extended-release”, “sustained-release” or “long-acting” opioids, are a highly potent form of opiate analgesic. The proposed advantage of long-acting opioids is that they stabilize medication levels, and provide around-the-clock analgesia. Long-acting opioids include: Morphine (MSContin®, Oramorph SR®, Kadian®, Avinza®), Oxycodone (Oxycontin®), Fentanyl (Duragesic Patch®), Hydromorphone (Palladone®).

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## Opioids, California Controlled Substance Utilization Review and Evaluation System (CURES) [DWC]

For patients with risk factors for drug abuse, a treating physician may consider utilizing the Controlled Substance Utilization Review and Evaluation System (CURES, <http://ag.ca.gov/bne/trips.htm>). CURES was established to automate the collection and analysis of all Schedule II controlled substance prescriptions issued in California. A physician may request a search for a Schedule II prescription history for a specific patient.

### Opioids, criteria for use

#### CRITERIA FOR USE OF OPIOIDS

##### Therapeutic Trial of Opioids

**1) Establish a Treatment Plan.** The use of opioids should be part of a treatment plan that is tailored to the patient. Questions to ask prior to starting therapy:

- (a) Are there reasonable alternatives to treatment, and have these been tried?
- (b) Is the patient likely to improve? Examples: Was there improvement on opioid treatment in the acute and subacute phases? Were there trials of other treatment, including non-opioid medications?
- (c) Is there likelihood of abuse or an adverse outcome? See Substance abuse (tolerance, dependence, addiction).
- (d) Ask about Red Flags indicating that opioids may not be helpful in the chronic phase:  
(1) Little or no relief with opioid therapy in the acute and subacute phases. (2) The patient has had a psychological evaluation and has been given a diagnosis of somatoform disorder. (3) The patient has been given a diagnosis in one of the particular diagnostic categories that have not been shown to have good success with opioid therapy: conversion disorder; somatization disorder; pain disorder associated with psychological factors (such as anxiety or depression).
- (e) When the patient is requesting opioid medications for their pain and inconsistencies are identified in the history, presentation, behaviors or physical findings, physicians and surgeons who make a clinical decision to withhold opioid medications should document the basis for their decision.

##### **2) Steps to Take Before a Therapeutic Trial of Opioids:**

- (a) Attempt to determine if the pain is nociceptive or neuropathic. Also attempt to determine if there are underlying contributing psychological issues. Neuropathic pain may require higher doses of opioids, and opioids are not generally recommended as a first-line therapy for some neuropathic pain.

## **CHRONIC PAIN MEDICAL TREATMENT GUIDELINES**

(b) A therapeutic trial of opioids should not be employed until the patient has failed a trial of non-opioid analgesics.

(c) Before initiating therapy, the patient should set goals, and the continued use of opioids should be contingent on meeting these goals.

(d) Baseline pain and functional assessments should be made. Function should include social, physical, psychological, daily and work activities, and should be performed using a validated instrument or numerical rating scale. See Function Measures.

(e) Pain related assessment should include history of pain treatment and effect of pain and function.

(f) Assess the likelihood that the patient could be weaned from opioids if there is no improvement in pain and function.

(g) The patient should have at least one physical and psychosocial assessment by the treating doctor (and a possible second opinion by a specialist) to assess whether a trial of opioids should occur. When subjective complaints do not correlate with imaging studies and/or physical findings and/or when psychosocial issue concerns exist, a second opinion with a pain specialist and a psychological assessment should be obtained.

(h) The physician and surgeon should discuss the risks and benefits of the use of controlled substances and other treatment modalities with the patient, caregiver or guardian.

(i) A written consent or pain agreement for chronic use is not required but may make it easier for the physician and surgeon to document patient education, the treatment plan, and the informed consent. Patient, guardian, and caregiver attitudes about medicines may influence the patient's use of medications for relief from pain. See Guidelines for Pain Treatment Agreement. This should include the consequences of non-adherence.

(j) Consider the use of a urine drug screen to assess for the use or the presence of illegal drugs.

### **3) Initiating Therapy**

(a) Intermittent pain: Start with a short-acting opioid trying one medication at a time.

(b) Continuous pain: extended-release opioids are recommended. Patients on this modality may require a dose of “rescue” opioids. The need for extra opioid can be a guide to determine the sustained release dose required.

(c) Only change 1 drug at a time.

(d) Prophylactic treatment of constipation should be initiated.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

(e) If partial analgesia is not obtained, opioids should be discontinued.

## 4) On-Going Management. Actions Should Include:

(a) Prescriptions from a single practitioner taken as directed, and all prescriptions from a single pharmacy.

(b) The lowest possible dose should be prescribed to improve pain and function.

(c) Office: Ongoing review and documentation of pain relief, functional status, appropriate medication use, and side effects. Pain assessment should include: current pain; the least reported pain over the period since last assessment; average pain; intensity of pain after taking the opioid; how long it takes for pain relief; and how long pain relief lasts. Satisfactory response to treatment may be indicated by the patient's decreased pain, increased level of function, or improved quality of life. Information from family members or other caregivers should be considered in determining the patient's response to treatment. The 4 A's for Ongoing Monitoring: Four domains have been proposed as most relevant for ongoing monitoring of chronic pain patients on opioids: pain relief, side effects, physical and psychosocial functioning, and the occurrence of any potentially aberrant (or nonadherent) drug-related behaviors. These domains have been summarized as the "4 A's" (analgesia, activities of daily living, adverse side effects, and aberrant drug-taking behaviors). The monitoring of these outcomes over time should affect therapeutic decisions and provide a framework for documentation of the clinical use of these controlled drugs. (Passik, 2000)

(d) Home: To aid in pain and functioning assessment, the patient should be requested to keep a pain diary that includes entries such as pain triggers, and incidence of end-of-dose pain. It should be emphasized that using this diary will help in tailoring the opioid dose. This should not be a requirement for pain management.

(e) Use of drug screening or inpatient treatment with issues of abuse, addiction, or poor pain control.

(f) Documentation of misuse of medications (doctor-shopping, uncontrolled drug escalation, drug diversion).

(g) Continuing review of overall situation with regard to nonopioid means of pain control.

(h) Consideration of a consultation with a multidisciplinary pain clinic if doses of opioids are required beyond what is usually required for the condition or pain does not improve on opioids in 3 months. Consider a psych consult if there is evidence of depression, anxiety or irritability. Consider an addiction medicine consult if there is evidence of substance misuse.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## 5) Recommended Frequency of Visits While in the Trial Phase (first 6 months):

(a) Every 2 weeks for the first 2 to 4 months

(b) Then at approximate 1 ½ to 2-month intervals

Note: According to the California Medical Board Guidelines for Prescribing Controlled Substances for Pain, patients with pain who are managed with controlled substances should be seen monthly, quarterly, or semiannually as required by the standard of care. (California, 1994)

**6) When to Discontinue Opioids:** See Opioid hyperalgesia. Also see Weaning of Medications. Prior to discontinuing, it should be determined that the patient has not had treatment failure due to causes that can be corrected such as under-dosing or inappropriate dosing schedule. Weaning should occur under direct ongoing medical supervision as a slow taper except for the below mentioned possible indications for immediate discontinuation. The patient should not be abandoned.

(a) If there is no overall improvement in function, unless there are extenuating circumstances

(b) Continuing pain with the evidence of intolerable adverse effects

(c) Decrease in functioning

(d) Resolution of pain

(e) If serious non-adherence is occurring

(f) The patient requests discontinuing

(g) Immediate discontinuation has been suggested for: evidence of illegal activity including diversion, prescription forgery, or stealing; the patient is involved in a motor vehicle accident and/or arrest related to opioids, illicit drugs and/or alcohol; intentional suicide attempt; aggressive or threatening behavior in the clinic. It is suggested that a patient be given a 30-day supply of medications (to facilitate finding other treatment) or be started on a slow weaning schedule if a decision is made by the physician to terminate prescribing of opioids/controlled substances.

(h) Many physicians will allow one “slip” from a medication contract without immediate termination of opioids/controlled substances, with the consequences being a re-discussion of the clinic policy on controlled substances, including the consequences of repeat violations.

(i) If there are repeated violations from the medication contract or any other evidence of abuse, addiction, or possible diversion it has been suggested that a patient show evidence

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of a consult with a physician that is trained in addiction to assess the ongoing situation and recommend possible detoxification. (Weaver, 2002)

(j) When the patient is requesting opioid medications for their pain and inconsistencies are identified in the history, presentation, behaviors or physical findings, physicians and surgeons who make a clinical decision to withhold opioid medications should document the basis for their decision.

## 7) When to Continue Opioids

(a) If the patient has returned to work

(b) If the patient has improved functioning and pain  
(Washington, 2002) (Colorado, 2002) (Ontario, 2000) (VA/DoD, 2003) (Maddox-AAPM/APS, 1997) (Wisconsin, 2004) (Warfield, 2004)

### Opioids for back pain

See Opioids for chronic pain.

### Opioids for chronic pain

*Recommendations for general conditions:*

-*Neuropathic pain:* Opioids have been suggested for neuropathic pain that has not responded to first-line recommendations (antidepressants, anticonvulsants). There are no trials of long-term use. There are virtually no studies of opioids for treatment of chronic lumbar root pain with resultant neuropathy. See Opioids for neuropathic pain.

- *Chronic back pain:* Appears to be efficacious but limited for short-term pain relief, and long-term efficacy is unclear (>16 weeks), but also appears limited. Failure to respond to a time-limited course of opioids has led to the suggestion of reassessment and consideration of alternative therapy. There is no evidence to recommend one opioid over another. In patients taking opioids for back pain, the prevalence of lifetime substance use disorders has ranged from 36% to 56% (a statistic limited by poor study design). Limited information indicated that up to one-fourth of patients who receive opioids exhibit aberrant medication-taking behavior. (Martell-Annals, 2007) (Chou, 2007) There are three studies comparing Tramadol to placebo that have reported pain relief, but this increase did not necessarily improve function. (Deshpande, 2007)

- *Headaches:* not recommended, in particular, due to the risk of medication overuse headache. (Lake, 2008) (Olesen, 2006) See Medication overuse headache.

- *Osteoarthritis:* Not recommended as a first-line therapy. Recommended on a trial basis for short-term use after there has been evidence of failure of first-line medication options such as acetaminophen or NSAIDs when there is evidence of moderate to severe pain. Also

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recommended for a trial if there is evidence of contraindications for use of first-line medications. Under study for long-term use as there is a lack of evidence to allow for a treatment recommendation. If used on a long-term basis, the criteria for use of opioids should be followed. See Opioids for osteoarthritis for citations.

- *Nociceptive pain*: Recommended as the standard of care for treatment of moderate or severe nociceptive pain (defined as pain that is presumed to be maintained by continual injury with the most common example being pain secondary to cancer).

- *Mechanical and compressive etiologies*: rarely beneficial.

Chronic pain can have a mixed physiologic etiology of both neuropathic and nociceptive components. In most cases, **analgesic** treatment should begin with acetaminophen, aspirin, and NSAIDs (as suggested by the WHO step-wise algorithm). When these drugs do not satisfactorily reduce pain, opioids for moderate to moderately severe pain may be added to (not substituted for) the less efficacious drugs. A major concern about the use of opioids for chronic pain is that most randomized controlled trials have been limited to a short-term period ( $\leq 70$  days). This leads to a concern about confounding issues such as tolerance, opioid-induced hyperalgesia, long-range adverse effects such as hypogonadism and/or opioid abuse, and the influence of placebo as a variable for treatment effect. (Ballantyne, 2006) (Furlan, 2006) Long-term, observational studies have found that treatment with opioids tends to provide improvement in function and minimal risk of addiction, but many of these studies include a high dropout rate (56% in a 2004 meta-analysis). (Kalso, 2004) There is also no evidence that opioids showed long-term benefit or improvement in function when used as treatment for chronic back pain. (Martell-*Annals*, 2007) Current studies suggest that the “upper limit of normal” for opioids prior to evaluation with a pain specialist for the need for possible continuation of treatment, escalation of dose, or possible weaning, is in a range from 120-180 mg morphine equivalents a day. (Ballantyne, 2006) (AMDG, 2007)

There are several proposed guidelines for the use of opioids for chronic non-malignant pain, but these have not been evaluated in clinical practice, and selection of the patient that will best respond to this treatment modality remains difficult. (Nicholas, 2006) (Stein, 2000) One of the most recent of these guidelines is the Agency Medical Director’s Group (AMDG) Guidelines from Washington State. This guideline includes an opioid dosing calculator. (AMDG, 2007)

*Outcomes measures*: It is now suggested that rather than simply focus on pain severity, improvements in a wide range of outcomes should be evaluated, including measures of functioning, appropriate medication use, and side effects. Measures of pain assessment that allow for evaluation of the efficacy of opioids and whether their use should be maintained include the following: current pain; the least reported pain over the period since last assessment; average pain; intensity of pain after taking the opioid; how long it takes for pain relief; and how long pain relief lasts. (Nicholas, 2006) (Ballantyne, 2006) A recent epidemiologic study found that opioid treatment for chronic non-malignant pain did not seem to fulfill any of key outcome goals including pain relief, improved quality of life, and/or improved functional capacity. (Eriksen, 2006)

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*Tolerance and addiction:* Opioid tolerance develops with the repeated use of opioids and brings about the need to increase the dose and may lead to sensitization. It is now clear that analgesia may not occur with open-ended escalation of opioids. It has also become apparent that analgesia is not always sustained over time, and that pain may be improved with weaning of opioids. (Ballantyne, 2006) (Ballantyne, 2003) See Substance abuse (tolerance, dependence, addiction).

*Behavior reinforcement:* A major concern in the use of opioids has been that a focus on this treatment without coordination with other modalities, such as psychosocial or behavioral therapy, may simply reinforce pain-related behavior, ultimately undermining rehabilitation that has been targeted at functional restoration. (Ontario, 2000) It has been shown that pain behavior can be reinforced by the prescribing of opioids, generally on an unintentional basis by the patient. (Fordyce, 1991)

*Overall treatment suggestions:* Current guidelines suggest the following:

- A trial of opioids as a first step in treatment, and the steps involved are outlined in the Criteria for Use of Opioids. The trial includes an initiation phase that involves selection of the opioid and initial dose. (VA/DoD, 2003)

- There is then a titration phase that includes dose adjustment. At this phase it may be determined that opioids are not achieving the desired outcomes, and they should be discontinued.

- The final stage is the maintenance phase. If pain worsens during this phase the differential to evaluate includes disease progression, increased activity, and/or new or increased pre-existing psychosocial factors that influence pain. In addition, the patient may develop hyperalgesia, tolerance, dependence or actual addiction.

(Washington, 2002) (Colorado, 2002) (Ontario, 2000) (VA/DoD, 2003) (Maddox-AAPM/APS, 1997) (Wisconsin, 2004) (Warfield, 2004) See Substance abuse (tolerance, dependence, addiction). See also Implantable pumps for narcotics. See Criteria for Use of Opioids.

### **Opioids for neuropathic pain**

Not recommended as a first-line therapy. Opioid analgesics and Tramadol have been suggested as a second-line treatment (alone or in combination with first-line drugs). A recent consensus guideline stated that opioids could be considered first-line therapy for the following circumstances: (1) prompt pain relief while titrating a first-line drug; (2) treatment of episodic exacerbations of severe pain; [&] (3) treatment of neuropathic cancer pain. (Dworkin, 2007) Response of neuropathic pain to drugs may differ according to the etiology of therapeutic pain. There is limited assessment of effectiveness of opioids for neuropathic pain, with short-term studies showing contradictory results and intermediate studies (8-70 days) demonstrating efficacy. (Eisenberg-Cochrane, 2006) (Eisenberg-JAMA, 2005) The results of short-term trials were mixed with respect to analgesia (less than 24 hours of treatment). Intermediate trials (average treatment duration of 28 days) showed statistical significance for reducing neuropathic pain by 20% to 30% (and 30% may be the threshold for describing a meaningful reduction of pain).

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*Treatment of chronic lumbar root pain:* A limitation of current studies is that there are virtually no repeated dose analgesic trials for neuropathy secondary to lumbar radiculopathy. A recent study that addressed this problem found that chronic lumbar radicular pain did not respond to either a tricyclic antidepressant or opioid in doses that have been effective for painful diabetic neuropathy or postherpetic neuralgia. Morphine was the least effective treatment (reducing leg and back pain by 1-7% compared to placebo). Sample size and drop out rate was a limitation. (Khoromi, 2007)

*Consideration of risks and side effects:* Opioids are considered a second-line treatment for several reasons: (1) head-to-head comparisons have found that opioids produce more side effects than TCAs and gabapentin; (2) long-term safety has not been systematically studied; (3) long-term use may result in immunological and endocrine problems (including hypogonadism); (4) treatment may be associated with hyperalgesia; & (5) opioid use is associated with misuse/abuse. Opioids may be a safer choice for patients with cardiac and renal disease than antidepressants or anticonvulsants. (Namaka, 2004)

*Specific drugs:* Morphine: superior to placebo in post-herpetic neuralgia, phantom limb and painful diabetic neuropathy (number needed to treat of 2.5). Oxycodone: post-herpetic neuralgia and painful diabetic neuropathy (NNT of 2.6). Tramadol: 2 trials of painful polyneuropathy on trial of post-herpetic neuropathy (overall NNT of 3.9). Other disease states that have been studied include post-amputation pain. (Finnerup, 2005) (Finnerup, 2007) (Wu, 2008)

### Opioids for osteoarthritis

Not recommended as a first-line therapy for osteoarthritis.

*Short-term use:* Recommended on a trial basis for short-term use after there has been evidence of failure of first-line non-pharmacologic and medication options (such as acetaminophen or NSAIDs) and when there is evidence of moderate to severe pain. Also recommended for a trial if there is evidence of contraindications for use of first-line medications. Weak opioids should be considered at initiation of treatment with this class of drugs (such as Tramadol, Tramadol/acetaminophen, hydrocodone and codeine), and stronger opioids are only recommended for treatment of severe pain under exceptional circumstances (oxycodone, oxycodone, hydromorphone, fentanyl, morphine sulfate). Benefits of opioids are limited by frequent side effects (including nausea, constipation, dizziness, somnolence and vomiting). (Stitik, 2006) (Avouac, 2007) (Zhang, 2008)

*Long-term use:* Under study for long-term use as there are no long-term trials. There is therefore a lack of evidence to allow for a treatment recommendation. If used on a long-term basis, the criteria for use of opioids should be followed. See Opioids, criteria for use.

*Opioids in general:* A recent meta-analysis found that opioids were more effective than placebo for reducing pain intensity. The benefit for physical function was small and was considered questionable for clinical relevance. Lack of benefit for function may be due to lack of anti-inflammatory effect for this class of medications and presence of side effects such as dizziness

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and drowsiness. Adverse events in general may limit the benefit of opioids as this same study found that out of every five patients that received opioids, one discontinued the medication due to an adverse event. These adverse events included epigastric pain, nausea, vomiting, constipation, dry mouth, dizziness, somnolence and headache. Weaker opioids were found to be less likely to produce adverse effects than stronger opioids such as oxycodone, Fentanyl or morphine. No conclusion can be made on how opioids compare to other available pharmacologic treatment due to limited studies. (Avouac, 2007)

Specific Opioids: Tramadol: A recent Cochrane review found that this drug decreased pain intensity, produced symptom relief and improved function for a time period of up to three months but the benefits were small (a 12% decrease in pain intensity from baseline). Adverse events often caused study participants to discontinue this medication, and could limit usefulness. There are no long-term studies to allow for recommendations for longer than three months. (Cepeda, 2006) Similar findings were found in an evaluation of a formulation that combines immediate-release vs. extended release Tramadol. Adverse effects included nausea, constipation, dizziness/vertigo and somnolence. (Burch, 2007)

### **Opioids, cancer pain vs. nonmalignant pain**

Definition. The use of opioids is well accepted in treating cancer pain, where nociceptive mechanisms are generally present due to ongoing tissue destruction, expected survival may be short, and symptomatic relief is emphasized more than functional outcomes. In chronic non-malignant pain, by contrast, tissue destruction has generally ceased. Expected survival in chronic pain is relatively long and return to a high level of function is a major goal of treatment. Therefore, approaches to pain developed in the context of malignant pain may not be transferable to chronic non-malignant pain. See Opioids for chronic pain.

### **Opioids, dealing with misuse & addiction**

Recommend that, if there are active signs of misuse, these concerns should be addressed immediately with the patient. If there are active signs of relapse to addiction, or new-onset addiction, these patients should be referred to an addictionologist immediately. It has been suggested that most chronic pain problems will not resolve while there is active and ongoing alcohol, illicit drug, or prescription drug abuse. (Weaver, 2002) Many physicians will allow one “slip” from a medication contract without immediate termination of opioids/controlled substances, with the consequences being a re-discussion of the clinic policy on controlled substances, including the consequences of repeat violations. If there are repeated violations from the medication contract or any other evidence of abuse, addiction, or possible diversion, it has been suggested that a patient show evidence of consultation with a physician trained in addiction treatment for assessment of the situation and possible detoxification. It is also suggested that a patient be given a 30-day supply of medications (to facilitate finding other treatment) or be started on a slow weaning schedule if a decision is made by the physician to terminate prescribing of opioids/controlled substances. (Weaver, 2002) When less serious warning signs arise, the following have been recommended (after making sure that there is no change in the patient’s condition that has introduced a need for additional treatment): (a) Initiate closer monitoring with more frequent visits; (b) Consider limitations in the amount of medication

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prescribed at any one time; & (c) Re-review the clinic policy on controlled substance use and the medication contract. (Weaver, 2002) (Chabel, 1997) In situations where there is dual diagnosis of opioid dependence and intractable pain, both of which are being treated with controlled substances, protections apply to California physicians and surgeons who prescribe controlled substances for intractable pain provided the physician complies with the requirements of the general standard of care and California Business and Professions Code section 2241.5. (California, 1994)

## Opioids, differentiation: dependence & addiction

Recommend screening to differentiate between dependence and addiction with opioids. The screening instruments below have been developed or are in the development stages to aid in differentiation between drug dependence and addiction. See also Opioids, red flags for addiction; Opioids, screening for risk of addiction; Opioids, patients at high-risk for misuse; & Substance abuse (tolerance, dependence, addiction).

1) *The Prescription Drug Use Questionnaire*: (Compton, 1998) This is a tool still in development, and it has not been validated. Variables found to be positive for individuals with a substance disorder were the following: (a) Belief by the individual that he/she was addicted; (b) Drug seeking behaviors (having more than one provider, increasing analgesic dose or frequency, calling in for early refills, and obtaining analgesics from the ER); (c) Using analgesics to relieve symptoms other than pain (insomnia, anxiety, depression); (d) supplementing analgesics with alcohol or other psychoactive drugs; & (e) Having been terminated from care by a physician or dentist. The three variables that correctly classified > 90% of addicts were: (1) A tendency to consider oneself addicted; (2) A preference for the route of administration; & (3) A tendency to increase opioid dose.

2) *Prescription opiate abuse in chronic pain patients (A NIH workshop summary)*: (Chabel, 1997) These criteria were developed to define prescription opiate abuse in patients using long-term opiates to treat chronic pain. Opiate abusers had at least three of the five of the following positive variables: (a) An overwhelming focus on opiate issues (persisting beyond the 3rd treatment session); (b) a pattern of early refills (3 or more) or escalating drug use in the absence of acute changes; (c) Multiple phone calls are made to the office for more opiates, early refills, or problems filling a previous prescription; (d) There is a pattern of prescription problems (lost medications, spilled medications, stolen medications); & (e) There is evidence of supplemental sources of opiates (multiple providers, emergency rooms, or illegal sources).

3) *Chelminski multi-disciplinary pain management program criteria*: (Chelminski, 2005) Criteria used to define serious substance misuse in a multi-disciplinary pain management program: (a) cocaine or amphetamines on urine toxicology screen (positive cannabinoid was not considered serious substance abuse); (b) procurement of opioids from more than one provider on a regular basis; (c) diversion of opioids; (d) urine toxicology screen negative for prescribed drugs on at least two occasions (an indicator of possible diversion); & (e) urine toxicology screen positive on at least two occasions for opioids not routinely prescribed.

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4) The Pain Medication Questionnaire (PMQ): (Adams, 2004) This is a screening instrument that is in development.

5) Portenoy criteria: (Portenoy, 1997) A compiled list of “aberrant drug-related behaviors.” Those behaviors that were identified as “probably more predictive” included: (a) forging prescriptions; (b) Stealing or borrowing drugs from others; (c) Frequent loss of prescriptions; & (d) Revisiting change to pain treatment (especially in light of adverse side effects).

6) Michna - Predicting aberrant drug behavior based on abuse history: (Michna, 2004) Six aberrant behaviors identified: (a) multiple unsanctioned escalations in dose; (b) lost or stolen medication; (c) frequent visits to the pain center or emergency room; (d) family members expressed concern about the patient’s use of opioids; & (e) excessive numbers of calls to the clinic. Other predictive variables included: (a) family history of substance abuse; (b) past problems with drugs and alcohol; (c) history of legal problems; (d) higher required dose of opioids for pain; (e) dependence on cigarettes; (f) psychiatric treatment history; (g) multiple car accidents; & (h) reporting fewer adverse symptoms from opioids.

### Opioids, dosing

Recommend that dosing not exceed 120 mg oral morphine equivalents per day, and for patients taking more than one opioid, the morphine equivalent doses of the different opioids must be added together to determine the cumulative dose. Use the appropriate factor below to determine the Morphine Equivalent Dose (MED) for each opioid. In general, the total daily dose of opioid should not exceed 120 mg oral morphine equivalents. Rarely, and only after pain management consultation, should the total daily dose of opioid be increased above 120 mg oral morphine equivalents. (Washington, 2007) There are other guidelines to consider, and actual maximum safe dose will be patient-specific and dependent on current and previous opioid exposure, as well as on whether the patient is using such medications chronically. When using single-agent opioid preparations, the dose should be slowly escalated until adequate pain relief is seen or side effects preclude further escalation. When using combination opioid products containing acetaminophen, aspirin, or ibuprofen, the dose limiting toxicity may be attributable to acetaminophen, aspirin, or ibuprofen respectively. The maximum amount of acetaminophen should be no more than 4 g/day. There are drawbacks to equivalency tables because they do not consider a recommended dose reduction for opioid cross-tolerance. Methadone conversion requires careful consideration because of its long half-life and unusual pharmacokinetic profile compared with most other opioids. In addition, converting methadone to morphine is not bidirectional. When switching from an established dose of methadone to another opioid, we must consider that measurable methadone serum levels will be around for days, so both drugs are now readily available, increasing the overall risk for opioid toxicity. (Fudin, 2008)

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## Opioid Dosing Calculator

### Morphine Equivalent Dose (MED) factor:

Codeine - 0.15  
Fentanyl transdermal (in mcg/hr) - 2.4  
Hydrocodone - 1  
Hydromorphone - 4  
Methadone, 41 to 60mg per day - 10  
Methadone, >60mg per day - 12  
Morphine - 1  
Oxycodone - 1.5  
Oxymorphone – 3

## Opioids, indicators for addiction

Recommend screening for indicators below. It is estimated that the prevalence of addictive disorders and/or serious substance misuse in patients with chronic pain may be as high as 30%. (Chelminski, 2005) The prevalence of current substance abuse disorders in patients with chronic back pain ranges from 3% to 43%, with a lifetime prevalence of 54% (but the author warns that these statistics are limited by poor study design and publication bias). (Martell-*Annals*, 2007) In studies of patients in methadone maintenance treatment as many as 44% of patients with chronic pain felt that the use of prescription opioids led to their problems with addiction. (Jamison, 2000) One particular problem is that in patients with substance abuse disorders and chronic pain the detrimental effects of drug use on lifestyle and psychosocial function may be ascribed to chronic pain instead of drug use, making the addiction disorder difficult to diagnose and treat. In addition, intermittent substance abuse withdrawal presents as and/or may cause hyperalgesia and facilitate pain. Another problem is that physicians are not well trained in diagnosing addiction or treating this condition. (Compton, 1998). (Savage, 2002) Clinical judgment by a physician trained in recognition of addiction is needed to determine if the patient actually has an addiction disorder. A history of an addiction disorder does not preclude a patient from being treated with opioids. (Savage, 1999) (Portenoy, 1996) See also Criteria for use of opioids; Opioids, screening for risk of addiction; Opioids, screening for dependence vs. addiction; Opioids, patients at high-risk for misuse; & Substance abuse (tolerance, dependence, addiction)

### Indicators and predictors of possible misuse of controlled substances and/or addiction:

- 1) Adverse consequences: (a) Decreased functioning, (b) Observed intoxication, (c) Negative affective state
  
- 2) Impaired control over medication use: (a) Failure to bring in unused medications, (b) Dose escalation without approval of the prescribing doctor, (c) Requests for early prescription refills, (d) Reports of lost or stolen prescriptions, (e) Unscheduled clinic appointments in “distress”, (f) Frequent visits to the ED, (g) Family reports of overuse of intoxication

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3) Craving and preoccupation: (a) Non-compliance with other treatment modalities, (b) Failure to keep appointments, (c) No interest in rehabilitation, only in symptom control, (d) No relief of pain or improved function with opioid therapy, (e) Overwhelming focus on opiate issues.

4) Adverse behavior: (a) Selling prescription drugs, (b) Forging prescriptions, (c) Stealing drugs, (d) Using prescription drugs in ways other than prescribed (such as injecting oral formulations), (e) Concurrent use of alcohol or other illicit drugs (as detected on urine screens), (f) Obtaining prescription drugs from non-medical sources

(Wisconsin, 2004) (Michna, 2004) (Chabal, 1997) (Portenoy, 1997)

## Opioids, long-term assessment

### CRITERIA FOR USE OF OPIOIDS

#### Long-term Users of Opioids (6-months or more)

##### 1) Re-assess

(a) Has the diagnosis changed?

(b) What other medications is the patient taking? Are they effective, producing side effects?

(c) What treatments have been attempted since the use of opioids? Have they been effective? For how long?

(d) Document pain and functional improvement and compare to baseline. Satisfactory response to treatment may be indicated by the patient's decreased pain, increased level of function, or improved quality of life. Information from family members or other caregivers should be considered in determining the patient's response to treatment. Pain should be assessed at each visit, and functioning should be measured at 6-month intervals using a numerical scale or validated instrument.

(e) Document adverse effects: constipation, nausea, vomiting, headache, dyspepsia, pruritis, dizziness, fatigue, dry mouth, sweating, hyperalgesia, sexual dysfunction, and sedation.

(f) Does the patient appear to need a psychological consultation? Issues to examine would include motivation, attitude about pain/work, return-to-work, social life including interpersonal and work-related relationships.

(g) Is there indication for a screening instrument for abuse/addiction. See Substance Abuse Screening.

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## 2) Strategy for maintenance

- (a) Do not attempt to lower the dose if it is working
- (b) Supplemental doses of break-through medication may be required for incidental pain, end-of dose pain, and pain that occurs with predictable situations. This can be determined by information that the patient provides from a pain diary or evaluation of additional need for supplemental medication.
- (c) The standard increase in dose is 25 to 50% for mild pain and 50 to 100% for severe pain (Wisconsin)

## 3) Visit Frequency

- (a) There is no set visit frequency. This should be adjusted to the patient's need for evaluation of adverse effects, pain status, and appropriate use of medication, with recommended duration between visits from 1 to 6 months.

(Washington, 2002) (Colorado, 2002) (Ontario, 2000) (VA/DoD, 2003) (Maddox-AAPM/APS, 1997) (Wisconsin, 2004) (Warfield, 2004)

## Opioids, pain treatment agreement

Recommended. A written consent or pain agreement for chronic use is not required but may make it easier for the physician and surgeon to document patient education, the treatment plan, and the informed consent. Patient, guardian, and caregiver attitudes about medicines may influence the patient's use of medications for relief from pain. This type of written document should be obtained prior to initiating opioid therapy. It should be discussed with the patient and family. This plan should be signed and dated and placed in the patient's chart, and include the following: (1) Goals of therapy, (2) Only one provider gives prescriptions, (3) Only one pharmacy dispenses prescriptions, (4) There will be a limit of number of medications, and dose of specific medications, (5) Medications are not to be altered without the prescribing doctor's permission, (6) Heavy machinery and automobile driving is not to occur until drug-induced sedation/drowsiness has cleared, (7) Refills are limited, and will only occur at appointments, (8) Treatment compliance must occur for all other modalities enlisted, (9) Urine drug screens may be required, (10) The patient must acknowledge that they are aware of potential adverse effects of the use of opioids including addiction, (11) Information about opioid management can be shared with family members and other providers as necessary, (12) If opioid use is not effective, the option of discontinuing this therapy may occur, (13) The consequence of non-adherence to the treatment agreement is outlined. (VA/DoD, 2003) (Heit, 2007)

## Opioids, patients at high-risk for misuse

See Opioids, steps to avoid misuse/addiction.

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## Opioids, psychological intervention

Recommended as an option to improve effectiveness of opioids for chronic pain. The following steps have been suggested to improve opioid treatment: (a) Provide ongoing education on both the benefits and limitations of opioid treatment. In particular, this should be based on the patient's experience with medication treatment and behavior regarding controlled substances in general. (b) Emphasize non-opioid care including self-management techniques. These may include relaxation, mindfulness meditation, acceptance, and distraction. (c) Emphasize realistic goals. (d) Avoid increasing dosages of medications to "chase pain." The result may ultimately be development of tolerance and/or hyperalgesia. (e) Encourage development of strategies for self-regulation of medication misuse. This may also include incorporation of a support group such as friends, family, an identified group (such as a 12-step group or group counseling), and/or individual counseling. (Naliboff, 2006)

## Opioids, red flags for addiction

See Opioids, indicators for addiction.

## Opioids, screening for dependence vs. addiction

See Opioids, differentiation: dependence & addiction.

## Opioids, screening for risk of addiction (tests)

Recommend screening for the risk of addiction prior to initiating opioid therapy. It is important to attempt to identify individuals who have the potential to develop aberrant drug use both prior to the prescribing of opioids and while actively undergoing this treatment. Most screening occurs after the claimant is already on opioids on a chronic basis, and consists of screens for aberrant behavior/misuse. Recommended screening instruments include the following:

1) *The CAGE Questionnaire*: (Brown, 1995) The most widely used screening tool prior to starting opioids is the CAGE questionnaire.

- a) Have you ever felt the need to cut down on your drinking or drug use?
- b) Have people annoyed you by criticizing your drinking or drug use?
- c) Have you ever felt bad or guilty about your drinking or drug use?
- d) Have you ever needed an eye opener the first thing in the morning to settle your nerves?

2) *Cyr-Wartman Screen*: (Cyr, 1988)

- a) Have you ever had a problem with alcohol (or drugs)?

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b) When was your last drink (or drugs)?

3) *Skinner Trauma Screen* (Skinner, 1984) Since your 18th birthday, have you

a) Had any fractures or dislocations to your bones or joints?

b) Been injured in a road traffic accident?

c) Injured your head?

d) Been injured in an assault or fight (excluding injuries from sports)?

e) Been injured after drinking?

4) *The Screener and Opioid Assessment for Patients with Pain (SOAPP)* (Akbik, 2006)

A brief self-report measure to capture important information in order to identify which chronic pain patients may be at risk for problems with long-term opioid medications. The cutoff score has been found with a positive answer of 8 or higher. Five factors were identified on factor analysis labeled 1) history of substance abuse, 2) legal problems, 3) craving medication, 4) heavy smoking, and 5) mood swings.

It is important to note that being at risk does not necessarily indicate that a patient will develop an addiction disorder, or is addicted.

5) *Opioid Risk Tool* (Kahan, 2006) A brief self-report tool that addresses five factors: (1) Family history of substance abuse; (2) Personal history of substance abuse; (3) Age (between 16 and 45 years); (4) History of preadolescent sexual abuse in females; & (5) Psychiatric history (ADD, OCD, bipolar, schizophrenia, and depression). The tool is gender specific. A history of an addiction disorder does not preclude a patient from being treated with opioids. (Savage 1999) (Portenoy, 1996)

### Opioids, specific drug list

Recommend specific dosage and cautions below. See also Opioids for overall classifications.

***Hydrocodone/Acetaminophen*** (*Anexsia®*, *Co-Gesic®*, *Hycet™*; *Lorcet®*, *Lortab®*; *Margesic-H®*, *Maxidone™*; *Norco®*, *Stagesic®*, *Vicodin®*, *Xodol®*, *Zydone®*; *generics available*): Indicated for moderate to moderately severe pain. Note: there are no FDA-approved hydrocodone products for pain unless formulated as a combination. *Side Effects*: See opioid adverse effects. *Analgesic dose*: The usual dose of 5/500mg is 1 or 2 tablets PO every four to six hours as needed for pain (Max 8 tablets/day). For higher doses of hydrocodone (>5mg/tab) and acetaminophen (>500mg/tab) the recommended dose is usually 1 tablet every four to six hours as needed for pain. Hydrocodone has a recommended maximum dose of 60mg/24 hours. The dose is limited by the dosage of acetaminophen, which should not exceed 4g/24 hours.

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**Hydrocodone/Ibuprofen** (*Vicoprofen®; generic available*): 7.5mg/200mg. *Side Effects*: See opioid adverse effects and NSAIDS. Note: Recommended for short term use only (generally less than 10 days). *Analgesic dose*: 1 tablet every 4-6 hours as needed for pain; maximum: 5 tablets/day (Product information, Abbott Laboratories).

**Codeine** (*Tylenol with Codeine®; generic available*): Codeine as a single active ingredient is classified by the DEA as a schedule II medication. Codeine in combination with acetaminophen is classified as schedule III. *Side Effects*: Common effects include CNS depression and hypotension. Drowsiness and constipation occur in > 10% of cases. Codeine should be used with caution in patients with a history of drug abuse. Tolerance, as well as psychological and physical dependence may occur. Abrupt discontinuation after prolonged use may result in withdrawal. (AHFS Drug Information, 2008) (Clinical Pharmacology, 2008) (Lexi-Comp, 2008). *Analgesic dose*: codeine - 15mg to 60mg per dose (Max 360mg/24hr), and acetaminophen 300mg to 1000mg per dose (Max 400mg/24hr). Doses may be given as needed up to every 4 hours. (Product information, Ortho-McNeil)

**Oxycodone immediate release** (*OxyIR® capsule; Roxicodone® tablets; generic available*), **Oxycodone controlled release** (*OxyContin®*): **[Boxed Warning]**: Oxycontin® Tablets are a controlled release formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. Oxycontin tablets are NOT intended for use as a prn analgesic. *Side Effects*: See opioid adverse effects. *Analgesic dose*: (Immediate release tablets) 5mg every 6 hours as needed. Controlled release: In opioid naive patients the starting dose is 10mg every 12 hours. Doses should be tailored for each individual patient, factoring in medical condition, the patient's prior opioid exposure, and other analgesics the patient may be taking. See full prescribing information to calculate conversions from other opioids. Note: See manufacturer's special instructions for prescribing doses of over 80mg and 160mg. Dietary caution: patients taking 160mg tablets should be advised to avoid high fat meals due to an increase in peak plasma concentration. (Product information, Purdue Pharma)

**Oxycodone/acetaminophen** (*Percocet®; generic available*): *Side Effects*: See opioid side effects and acetaminophen. *Analgesic dose*: Dosage based on oxycodone content and should be administered every 4 to 6 hours as needed for pain. Initially 2.5 to 5 mg PO every 4 to 6 hours prn. Note: Maximum daily dose is based on acetaminophen content (Maximum 4000mg/day). For more severe pain the dose (based on oxycodone) is 10-30mg every 4 to 6 hours prn pain. Dose should be reduced in patients with severe liver disease.

**Levorphanol** (*Levo-Dromoran®; generic available*): 2mg tablets. Used for moderate to severe pain, when an opioid is appropriate for therapy. Levorphanol has been shown to be effective for neuropathic pain. (Prommer 2007) Levorphanol is 4 to 8 times as potent as morphine and it has a much longer half-life. *Side Effects*: See opioid adverse effects. *Analgesic dose*: The usual starting dose is 2mg PO, which may be repeated in 6 to 8 hours. Note: Assess patient for signs of hypoventilation and excessive sedation before continuing subsequent doses. Patients who tolerate dosing and need further pain management may take 3mg PO every 6 to 8 hours. Note: Levorphanol is not recommended for breakthrough pain. (Prommer 2007)

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**Oxymorphone** (*Opana*®), *Oxymorphone Extended Release* (*Opana ER*®), *no available generic*: [Boxed Warnings]: *Opana ER*® is not intended for prn use. Patients are to avoid alcohol while on *Opana ER*® due to increased (possibly fatal) plasma levels. *Side Effects*: See opioid adverse effects. Immediate release and extended release tablets should be taken 1 hour before or 2 hours after eating. *Analgesic dose*: (Immediate release) in opioid-naive patients the starting dose is 10-20mg PO every 4 to 6 hours as needed. Patients may be started at doses of 5mg if appropriate (e.g., renal impairment). Refer to full prescribing information for calculating conversions from other opioids. Note: It is not recommended to begin therapy at doses higher than 20mg due to adverse effects. (Extended release tablets) Opioid-naive patients should initially begin on 5mg every 12 hours around the clock. It is recommended that doses be individually titrated in increments of 5 to 10mg every 12 hours for 3 to 7 days. (Product information, Ethex Pharmaceuticals)

**Hydromorphone** (*Dilaudid*®; *generic available*): 2mg, 4mg, 8mg. *Side Effects*: Respiratory depression and apnea are of major concern. Patients may experience some circulatory depression, respiratory arrest, shock and cardiac arrest. The more common side effects are dizziness, sedation, nausea, vomiting, sweating, dry mouth and itching. (Product Information, Abbott Labs 2006) *Analgesic dose*: Usual starting dose is 2mg to 4mg PO every 4 to 6 hours. A gradual increase may be required, if tolerance develops.

**Methadone** (*Dolophine*®, *Methadose*® oral dosage forms, *generic available*): *Side Effects*: See methadone adverse effects. *Analgesic dose*: For moderate to severe pain the initial oral dose (opioid naive) is 2.5mg to 10mg every 8 to 12 hours. However, a smaller dosing interval (every 4 to 12 hours) may be needed to produce adequate pain relief.

**Morphine sulfate**, *Morphine sulfate ER, CR* (*Avinza*®; *Kadian*®; *MS Contin*®; *Oramorph SR*®; *generic available, except extended release capsules*): *Side Effects*: See opioid adverse effects. *Analgesic dose*: Controlled, extended and sustained release preparations should be reserved for patients with chronic pain, who are in need of continuous treatment. *Avinza*® - morphine sulfate extended release for once daily dosing. The 60mg, 90mg and 120mg capsules are for opioid tolerant patients only. *Kadian*® - (extended release capsules) May be dosed once or twice daily. The 100mg and 200mg capsules are intended for opioid tolerant patients only. *MS Contin*® - (controlled release tablets) Doses should be individually tailored for each patient.

**Fentanyl transdermal** (*Duragesic*®; *generic available*): Indicated for management of persistent chronic pain, which is moderate to severe requiring continuous, around-the-clock opioid therapy. The pain cannot be managed by other means (e.g., NSAIDs). Note: *Duragesic*® should only be used in patients who are currently on opioid therapy for which tolerance has developed. The patches should be applied to INTACT skin only. *Side Effects*: See opioid adverse effects. *Analgesic dose*: The previous opioid therapy for which tolerance has occurred should be at least equivalent to fentanyl 25mcg/h. Patches are worn for a 72 hour period. (Product information, Purdue Pharma)

**Tramadol** (*Ultram*®; *Ultram ER*®; *generic available in immediate release tablet*): Tramadol is a synthetic opioid affecting the central nervous system. Tramadol is not classified as a controlled substance by the DEA. *Side Effects*: Dizziness, nausea, constipation, headache, somnolence,

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flushing, pruritus, vomiting, insomnia, dry mouth, and diarrhea. Tramadol may increase the risk of seizure especially in patients taking SSRIs, TCAs and other opioids. Do not prescribe to patients that at risk for suicide or addiction. Warning: Tramadol may produce life-threatening serotonin syndrome, in particular when used concomitantly with SSRIs, SNRIs, TCAs, and MAOIs, and triptans or other drugs that may impair serotonin metabolism. *Analgesic dose:* Tramadol is indicated for moderate to severe pain. The immediate release formulation is recommended at a dose of 50 to 100mg PO every 4 to 6 hours (not to exceed 400mg/day). This dose is recommended after titrating patients up from 100mg/day, with dosing being increased every 3 days as tolerated. For patients in need of immediate pain relief, which outweighs the risk of non-tolerability the initial starting dose, may be 50mg to 100mg every 4 to 6 hours (max 400mg/day). Ultram ER®: Patient currently not on immediate release tramadol should be started at a dose of 100mg once daily. The dose should be titrated upwards by 100mg increments if needed (Max dose 300mg/day). Patients currently on immediate release tramadol, calculate the 24-hour dose of IR and initiate a total daily dose of ER rounded to the next lowest 100mg increment (Max dose 300mg/day). (Product information, Ortho-McNeil 2003) (Lexi-Comp, 2008)

*Propoxyphene hydrochloride (Darvon®; generic available), Propoxyphene napsylate (Darvon-N®), Propoxyphene/Apap (Darvocet-N; generic available): Side Effects:* See propoxyphene and acetaminophen. *Analgesic dose:* Propoxyphene Hcl is available in 65 mg capsule and the dose is 65mg every 3 to 4 hours as needed. Maximum daily dose is 390mg. Propoxyphene napsylate is available in 100mg tablets which are to be given 100mg every 4 hours as needed (Maximum daily dose is 600mg). Propoxyphene-N/Apap is available as 50mg/650mg and 100mg/650mg. 50mg/650mg: 1 or 2 tablets PO every 4 hours as needed for pain. 100mg/650mg: 1 PO every 4 to 6 hours as needed for pain. Max daily doses should not exceed that of propoxyphene (600mg) and acetaminophen (4000mg). (Clinical Pharmacology, 2008)

### Opioids, state medical boards guidelines

The Federation of State Medical Boards Model Guidelines for the Use of Controlled Substances for the Treatment of Pain say State medical boards recognize undertreatment of pain as a public health priority. Underprescribing pain medications is considered as much a breach of the appropriate standard of care as overprescribing. (Federation, 2004) See also individual state guidelines, for example the California Medical Board Guidelines for Prescribing Controlled Substances for Pain. (California, 1994)

### Opioids, steps to avoid misuse/addiction

The following are steps to avoid misuse of opioids, and in particular, for those at high risk of abuse:

- a) Opioid therapy contracts. See Guidelines for Pain Treatment Agreement.
- b) Limitation of prescribing and filling of prescriptions to one pharmacy.
- c) Frequent random urine toxicology screens.

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- d) Frequent evaluation of clinical history, including questions about cravings for the former drug of abuse (a potential early sign of relapse).
- e) Frequent review of medications (including electronic medical record evaluation when available and pill counts at each visit, brought in the original bottle from the pharmacy).
- f) Communication with pharmacists.
- g) Communication with previous providers and other current providers, with evidence of obtaining medical records. (It has been recommended that opioids should not be prescribed on a first visit until this step has been undertaken.)
- h) Evidence of participation in a recovery program (12-step or follow-up with a substance abuse counselor), such as speaking to his/her sponsor for the 12-step program.
- i) Establishment of goals of treatment that can be realistically achieved.
- j) Initiation of appropriate non-opioid adjunct medications and exercise programs.
- k) Utilize careful documentation, and in particular, that which is recommended in the State in which opioids are prescribed.
- l) Incorporate family and friends for support and education.

(Chabel,1997) (Michna,2004) (Weaver,2002)

### **Opioids, weaning of medications**

See Weaning of medications.

### **Opioid hyperalgesia**

Recommend screening and treatment as indicated below.

Definition: Patients who receive opiate therapy sometimes develop unexpected changes in their response to opioids. This may include the development of abnormal pain (hyperalgesia), a change in pain pattern, or persistence in pain at higher levels than expected. These types of changes occur in spite of continued incremental dose increases of medication. Opioids in this case actually increase rather than decrease sensitivity to noxious stimuli. It is important therefore to note that a decrease in opioid efficacy should not always be treated by increasing the dose, but may actually require weaning. (Chang, 2007)

Diagnosis: How to diagnose:

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- (1) Attempt to determine if pain has increased over that, which was pre-existing (in the absence of apparent disease progression).
- (2) Attempt to determine if the patient has previously responded to opioids but now has worsening pain.
- (3) Attempt to determine if the patient has never had improved pain with opioids.
- (4) If disease progression is ruled out, is there evidence of possible opioid tolerance or is this opioid hyperalgesia.
- (5) Evaluate pain: In cases of opioid hyperalgesia pain may spread and become more diffuse and less well-defined in quality, beyond what would be expected from the preexisting pain state. This is generally not an acute but is an insidious process.
- (6) Psychological issues such as secondary gain, exacerbation of underlying depression or anxiety, and the development of addictive disease should also be ruled out.

Treatment: Suggested treatment for patients with increasing pain (assumes that the patient has had improvement with opioids at some point):

- (1) It is not unreasonable to give a trial of opioid dose escalation to see if pain and function improves. If pain improves, the diagnosis is probable tolerance. If pain does not improve or worsens, this may be evidence of opioid hyperalgesia and the opioid dose should be reduced or actually weaned.
- (2) Opioid rotation is another option.
- (3) Use of adjuvant pain medications is recommended when there is evidence of either tolerance or hyperalgesia.
- (4) Further evaluation by a specialist with additional expertise in psychiatry, pain medicine, or addiction medicine should be considered when there is evidence of no improvement of pain with increasing doses of opioids.

### **Opioid pumps**

See Implantable drug-delivery systems (IDDSs).

### **Oral morphine**

Not recommended as a primary treatment for persistent pain. The use of opioid analgesics for chronic non-cancer pain is controversial. One randomized controlled trial found that oral morphine may confer analgesic benefit with a low risk of addiction but is unlikely to yield psychological or functional improvement. (Moulin, 1996) See also Opioids.

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## **Oxcarbazepine (Trileptal®)**

See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific **Oxcarbazepine** listing.

## **Oxycodone**

Oxycodone is a potentially addictive opioid analgesic medication, and it is a Schedule II controlled substance. See Opioids.

## **Oxycontin® (oxycodone)**

OxyContin® is the brand name of a time-release formula of the analgesic chemical oxycodone, produced by the pharmaceutical company Purdue Pharma. See Opioids. Note: This drug was recently included in a list of 20 medications identified by the FDA's Adverse Event Reporting System, that are under FDA investigation. (FDA, 2008)

## **Pain management programs**

See Chronic pain programs.

## **Percocet® (oxycodone & acetaminophen)**

Percocet® is the brand name of an oxycodone and acetaminophen combination drug, produced by Endo Pharmaceuticals. See Opioids.

## **Percutaneous electrical nerve stimulation (PENS)**

Not recommended as a primary treatment modality, but a trial may be considered, if used as an adjunct to a program of evidence-based functional restoration, after other non-surgical treatments, including therapeutic exercise and TENS, have been tried and failed or are judged to be unsuitable or contraindicated. There is a lack of high quality evidence to prove long-term efficacy. (Ghonaime-JAMA, 1999) (Yokoyama, 2004) Percutaneous electrical nerve stimulation (PENS) is similar in concept to transcutaneous electrical nerve stimulation (TENS) but differs in that needles are inserted to a depth of 1 to 4 cm either around or immediately adjacent to the nerve serving the painful area and then stimulated. PENS is generally reserved for patients who fail to get pain relief from TENS, apparently due to obvious physical barriers to the conduction of the electrical stimulation (e.g., scar tissue, obesity). PENS must be distinguished from acupuncture with electrical stimulation. In PENS the location of stimulation is determined by proximity to the pain. (BlueCross BlueShield, 2004) (Aetna, 2005) This RCT concluded that both PENS and therapeutic exercise for older adults with chronic low back pain significantly reduced pain. (Weiner, 2008) See also TENS.

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## **Percutaneous neuromodulation therapy (PNT)**

Not recommended. Percutaneous neuromodulation therapy (PNT) is considered investigational. Percutaneous neuromodulation therapy is a variant of PENS in which up to 10 fine filament electrodes are temporarily placed at specific anatomical landmarks in the back. Treatment regimens consist of 30-minute sessions, once or twice a week for eight to ten sessions. Percutaneous Neuromodulation Therapy™ (Vertis Neurosciences) received approval to market by the U.S. Food and Drug Administration (FDA) through the 510(k) process in 2002. The labeled indications reads as follows: "Percutaneous neuromodulation therapy (PNT) is indicated for the symptomatic relief and management of chronic or intractable pain and/or as an adjunct treatment in the management of post-surgical pain and post-trauma pain." (Condon, 2002) (BlueCross BlueShield, 2004)

## **Phentolamine infusion test**

Recommended as indicated below. An intravenous infusion of phentolamine, an alpha 2 blocker, results in generalized systemic sympatholysis. The infusion begins with intravenous saline for placebo control. For a positive response, pain relief should be 50 percent or greater and associated with functional improvement. This test aids in the diagnosis of SMP (Sympathetically maintained pain). (Colorado, 2002) See also Sympathetically maintained pain (SMP).

## **Phenytoin (Dilantin®)**

See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Phenytoin listing.

## **Phototherapy**

See Low level laser therapy (LLLT).

## **Physical Medicine**

Recommended as indicated below. Passive therapy (those treatment modalities that do not require energy expenditure on the part of the patient) can provide short term relief during the early phases of pain treatment and are directed at controlling symptoms such as pain, inflammation and swelling and to improve the rate of healing soft tissue injuries. They can be used sparingly with active therapies to help control swelling, pain and inflammation during the rehabilitation process. Active therapy is based on the philosophy that therapeutic exercise and/or activity are beneficial for restoring flexibility, strength, endurance, function, range of motion, and can alleviate discomfort. Active therapy requires an internal effort by the individual to complete a specific exercise or task. This form of therapy may require supervision from a therapist or medical provider such as verbal, visual and/or tactile instruction(s). Patients are instructed and expected to continue active therapies at home as an extension of the treatment process in order to maintain improvement levels. Home exercise can include exercise with or without mechanical assistance or resistance and functional activities with assistive devices. (Colorado, 2002) (Airaksinen, 2006) Patient-specific hand therapy is very important in reducing

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swelling, decreasing pain, and improving range of motion in CRPS. (Li, 2005) The use of active treatment modalities (e.g., exercise, education, activity modification) instead of passive treatments is associated with substantially better clinical outcomes. In a large case series of patients with low back pain treated by physical therapists, those adhering to guidelines for active rather than passive treatments incurred fewer treatment visits, cost less, and had less pain and less disability. The overall success rates were 64.7% among those adhering to the active treatment recommendations versus 36.5% for passive treatment. (Fritz, 2007)

## **Physical Medicine Guidelines –**

Allow for fading of treatment frequency (from up to 3 visits per week to 1 or less), plus active self-directed home Physical Medicine.

**Myalgia and myositis, unspecified (ICD9 729.1):** 9-10 visits over 8 weeks

**Neuralgia, neuritis, and radiculitis, unspecified (ICD9 729.2)**

8-10 visits over 4 weeks

**Reflex sympathetic dystrophy (CRPS) (ICD9 337.2):**

24 visits over 16 weeks

## **Physical Therapy (PT)**

See Physical Medicine

## **Power mobility devices (PMDs)**

Not recommended if the functional mobility deficit can be sufficiently resolved by the prescription of a cane or walker, or the patient has sufficient upper extremity function to propel a manual wheelchair, or there is a caregiver who is available, willing, and able to provide assistance with a manual wheelchair. Early exercise, mobilization and independence should be encouraged at all steps of the injury recovery process, and if there is any mobility with canes or other assistive devices, a motorized scooter is not essential to care.

## **Pregabalin (Lyrica®)**

Pregabalin (Lyrica®) has been documented to be effective in treatment of diabetic neuropathy and postherpetic neuralgia, has FDA approval for both indications, and is considered first-line treatment for both. Pregabalin was also approved to treat fibromyalgia. See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Pregabalin listing for more information and references.

## **Prialt®**

See Ziconotide (Prialt®).

## **Prolotherapy**

Not recommended. Prolotherapy describes a procedure for strengthening lax ligaments by injecting proliferating agents/sclerosing solutions directly into torn or stretched ligaments or

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tendons or into a joint or adjacent structures to create scar tissue in an effort to stabilize a joint. Agents used with prolotherapy have included zinc sulfate, psyllium seed oil, combinations of dextrose, glycerine and phenol, or dextrose alone. "Proliferatives" act to promote tissue repair or growth by prompting release of growth factors, such as cytokines, or increasing the effectiveness of existing circulating growth factors. Prolotherapy has been investigated as a treatment of various etiologies of pain, including arthritis, degenerative disc disease, fibromyalgia, tendinitis, and plantar fasciitis. In all studies the effects of prolotherapy did not significantly exceed placebo effects. (Dechow, 1999) (Reeves, 2000) (Yelland, 2004) (BlueCross BlueShield, 2006)

### **Propoxyphene (Darvon®)**

Recommended as an option for mild to moderate pain, as indicated below. The most common brand names are Darvon® (propoxyphene hydrochloride), Darvon-N® (propoxyphene napsylate) or in combination with acetaminophen as Darvocet®. Generic available. Propoxyphene is structurally related to methadone. This is a synthetic opiate agonist that is ½ to 1/3 as potent as codeine. High doses are limited due to adverse effects including toxic psychosis. It is FDA approved for mild to moderate pain.

*Dosage:* Neither of these medications is recommended for the elderly. Dosage should be reduced for patients with hepatic or renal impairment. *Propoxyphene hydrochloride:* The standard adult dose is 65 mg every 3-4 hours. The maximum dose should not exceed 390 mg/day. *Propoxyphene napsylate:* The standard adult dose is 100 mg every 4 hours with a maximum dose of 600 mg/day.

*Side effects:* sedation, nausea & vomiting and dizziness. Overuse can cause drug-rebound headache. Dependence can occur as well as mild withdrawal. *FDA warnings:* Do not prescribe to patients that are suicidal or addiction-prone. Prescribe with caution in patients taking tranquilizers or antidepressants, and in patients who use alcohol in excess. A major cause of drug-related deaths is secondary to propoxyphene alone or in combination with other CNS depressants. *Other warnings:* Use this drug with caution for patients that are dependent on opioids. Propoxyphene will not support morphine dependence. Sudden substitution may produce acute withdrawal.

*Overdose:* Adverse effects include coma and respiratory depression as well as circulatory collapse. Complications such as irreversible brain damage and death may occur within one hour. These rapid, serious complications of overdose are due, in part, to the difficulty of reversal with naloxone (due to high tissue concentration and long half-life of metabolites). (Clinical Pharmacology, 2008) (Micromedix, 2008) (Lexi-Comp, 2008) (AHFS Drug Information, 2008)

### **Psychological evaluations**

Recommended. Psychological evaluations are generally accepted, well-established diagnostic procedures not only with selected use in pain problems, but also with more widespread use in chronic pain populations. Diagnostic evaluations should distinguish between conditions that are preexisting, aggravated by the current injury or work related. Psychosocial evaluations should determine if further psychosocial interventions are indicated. The interpretations of the

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evaluation should provide clinicians with a better understanding of the patient in their social environment, thus allowing for more effective rehabilitation. (Main-BMJ, 2002) (Colorado, 2002) (Gatchel, 1995) (Gatchel, 1999) (Gatchel, 2004) (Gatchel, 2005) For the evaluation and prediction of patients who have a high likelihood of developing chronic pain, a study of patients who were administered a standard battery psychological assessment test found that there is a psychosocial disability variable that is associated with those injured workers who are likely to develop chronic disability problems. (Gatchel, 1999) Childhood abuse and other past traumatic events were also found to be predictors of chronic pain patients. (Goldberg, 1999) Another trial found that it appears to be feasible to identify patients with high levels of risk of chronic pain and to subsequently lower the risk for work disability by administering a cognitive-behavioral intervention focusing on psychological aspects of the pain problem. (Linton, 2002) Other studies and reviews support these theories. (Perez, 2001) (Pulliam, 2001) (Severeijns, 2001) (Sommer, 1998) In a large RCT the benefits of improved depression care (antidepressant medications and/or psychotherapy) extended beyond reduced depressive symptoms and included decreased pain as well as improved functional status. (Lin-JAMA, 2003) See "Psychological Tests Commonly Used in the Assessment of Chronic Pain Patients" from the Colorado Division of Workers' Compensation, which describes and evaluates the following 26 tests: (1) BHI 2<sup>nd</sup> ed -Battery for Health Improvement, (2) MBHI - Millon Behavioral Health Inventory [has been superceded by the MBMD following, which should be administered instead], (3) MBMD - Millon Behavioral Medical Diagnostic, (4) PAB - Pain Assessment Battery, (5) MCMI-111 - Millon Clinical Multiaxial Inventory, (6) MMPI-2 - Minnesota Inventory, (7) PAI - Personality Assessment Inventory, (8) BBHI 2 - Brief Battery for Health Improvement, (9) MPI - Multidimensional Pain Inventory, (10) P-3 - Pain Patient Profile, (11) Pain Presentation Inventory, (12) PRIME-MD - Primary Care Evaluation for Mental Disorders, (13) PHQ - Patient Health Questionnaire, (14) SF 36, (15) SIP - Sickness Impact Profile, (16) BSI - Brief Symptom Inventory, (17) BSI 18 - Brief Symptom Inventory, (18) SCL-90 - Symptom Checklist, (19) BDI-II - Beck Depression Inventory, (20) CES-D - Center for Epidemiological Studies Depression Scale, (21) PDS - Post Traumatic Stress Diagnostic Scale, (22) Zung Depression Inventory, (23) MPQ - McGill Pain Questionnaire, (24) MPQ-SF - McGill Pain Questionnaire Short Form, (25) Oswestry Disability Questionnaire, (26) Visual Analogue Pain Scale – VAS. (Bruns, 2001)

### **Psychological evaluations, IDDS & SCS (intrathecal drug delivery systems & spinal cord stimulators)**

Recommended pre-intrathecal drug delivery systems (IDDS) and spinal cord stimulator (SCS) trial.

### **Psychological treatment**

Recommended for appropriately identified patients during treatment for chronic pain. Psychological intervention for chronic pain includes setting goals, determining appropriateness of treatment, conceptualizing a patient's pain beliefs and coping styles, assessing psychological and cognitive function, and addressing co-morbid mood disorders (such as depression, anxiety, panic disorder, and posttraumatic stress disorder). Cognitive behavioral therapy and self-regulatory treatments have been found to be particularly effective. Psychological treatment

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incorporated into pain treatment has been found to have a positive short-term effect on pain interference and long-term effect on return to work. The following “stepped-care” approach to pain management that involves psychological intervention has been suggested:

Step 1: Identify and address specific concerns about pain and enhance interventions that emphasize self-management. The role of the psychologist at this point includes education and training of pain care providers in how to screen for patients that may need early psychological intervention.

Step 2: Identify patients who continue to experience pain and disability after the usual time of recovery. At this point a consultation with a psychologist allows for screening, assessment of goals, and further treatment options, including brief individual or group therapy.

Step 3: Pain is sustained in spite of continued therapy (including the above psychological care). Intensive care may be required from mental health professions allowing for a multidisciplinary treatment approach. See also Multi-disciplinary pain programs. See also ODG Cognitive Behavioral Therapy (CBT) Guidelines. (Otis, 2006) (Townsend, 2006) (Kerns, 2005) (Flor, 1992) (Morley, 1999) (Ostelo, 2005)

## **Pulsed radiofrequency treatment (PRF)**

Not recommended. Pulsed radiofrequency treatment (PRF) has been investigated as a potentially less harmful alternative to radiofrequency (RF) thermal neurolytic destruction (thermocoagulation) in the management of certain chronic pain syndromes such as facet joint pain and trigeminal neuralgia. Pulsed radiofrequency treatment is considered investigational/not medically necessary for the treatment of chronic pain syndromes. (BlueCross, 2005) A decrease in pain was observed in patients with herniated disc and spinal stenosis, but not in those with failed back surgery syndrome. However, this option does not appear to be an ideal modality of treatment for lumbar radicular pain because neurodestructive methods for the treatment of neuropathic pain are in principle generally considered inappropriate. (Abejón, 2007)

## **Pumps, implantable**

See Implantable drug-delivery systems (IDDSs).

## **Pycnogenol (maritime pine bark) [DWC]**

Pycnogenol (maritime pine bark) is not recommended for chronic pain.

## **Rapid detox**

Not recommended. Gradual weaning is recommended for long-term opioid users because opioids cannot be abruptly discontinued without probable risk of withdrawal symptoms. The data supporting the safety and effectiveness of opioid antagonist agent detoxification under sedation or general anesthesia is limited, and adequate safety has not been established. Given that the adverse events are potentially life threatening, the value of antagonist-induced withdrawal under

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heavy sedation or anesthesia is not supported. The high cost of anesthesia-based approaches, both in monetary terms and use of scarce intensive care resources, suggest that this form of treatment should not be pursued. (McCabe, 2000) (Gowing-Cochrane, 2006) The American Society of Addiction Medicine (ASAM) issued a revised public policy statement (2005) regarding rapid and ultra-rapid opioid detoxification. The policy recommendations state that opioid detoxification should be part of an integrated continuum of services that promotes ongoing recovery from addiction. Additional policy recommendations state that ultra-rapid detoxification is a procedure with uncertain risks and benefits, and its use in the clinical setting is not supported. (ASAM, 2005) This treatment is not generally covered in the group health arena. (Aetna, 2006) (Blue Cross/Blue Shield, 2006) (CIGNA, 2006)

### **Regional sympathetic blocks (stellate ganglion block, thoracic sympathetic block, & lumbar sympathetic block)**

Recommendations are generally limited to diagnosis and therapy for CRPS. See CRPS, sympathetic and epidural blocks for specific recommendations for treatment. Also see CRPS, diagnostic criteria; CRPS, medications; & CRPS.

*Stellate ganglion block (SGB) (Cervicothoracic sympathetic block):* There is limited evidence to support this procedure, with most studies reported being case studies. The one prospective double-blind study (of CRPS) was limited to 4 subjects. *Anatomy:* Sympathetic flow to the head, neck and most of the upper extremities is derived from the upper five to seven thoracic spinal segments. The stellate ganglion is formed by a fusion of the inferior and first thoracic sympathetic ganglia in 80% of patients. In the other 20%, the first thoracic ganglion is labeled the stellate ganglion. The upper extremity may also be innervated by branches for Kuntz's nerves, which may explain inadequate relief of sympathetic related pain. *Proposed Indications:* This block is proposed for the diagnosis and treatment of sympathetic pain involving the face, head, neck, and upper extremities. Pain: CRPS; Herpes Zoster and post-herpetic neuralgia; Frostbite. Circulatory insufficiency: Traumatic/embolic occlusion; Post-reimplantation; Post-embolic vasospasm; Raynaud's disease; Vasculitis; Scleroderma. *Testing for an adequate block:* Adequacy of a sympathetic block should be recorded. A Horner's sign (ipsilateral ptosis, miosis, anhydrosis conjunctival engorgement, and warmth of the face) indicates a sympathetic block of the head and face. It does not indicate a sympathetic block of the upper extremity. The latter can be measured by surface temperature difference (an increase in temperature on the side of the block). Somatic block of the arm should also be ruled out (the incidence of brachial plexus nerve block is ~ 10%). Complete sympathetic blockade can be measured with the addition of tests of abolition of sweating and of the sympathogalvanic response. Documentation of motor and/or sensory block should occur. *Complications:* Incidental recurrent laryngeal nerve block or superior laryngeal nerve block, resulting in hoarseness and subjective shortness of breathe; Brachial plexus block; Intravascular injection; Intrathecal, subdural or epidural injection; Puncture of the pleura with pneumothorax; Bleeding and hematoma. There appears to be a positive correlation between efficacy and how soon therapy is initiated (as studied in patients with CRPS of the hand). Duration of symptoms greater than 16 weeks before the initial SGB and/or a decrease in skin perfusion of 22% between the normal and affected hands adversely affected the efficacy of SGB therapy. (Ackerman, 2006) (Sayson, 2004) (Grabow, 2005) (Colorado, 2006) (Price, 1998) (Day, 2008) (Nader, 2005) See also Stellate ganglion block.

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*Thoracic Sympathetic Blocks:* Not recommended due to a lack of literature to support effectiveness. Utilized for sympathetic blocks of the upper extremity in the 20% of individuals with innervation of the upper extremity by Kuntz's nerves (nerves from the 2<sup>nd</sup> and 3<sup>rd</sup> thoracic sympathetic ganglia bypass the stellate ganglion and directly join the brachial plexus). *Proposed Indications:* CRPS, peripheral neuropathy, brachial plexalgia, sympathetically maintained pain and vascular disorders. (Day, 2008) *Complications:* neuraxial injection; intravascular injection; nerve injury; pneumothorax.

*Lumbar Sympathetic Blocks:* There is limited evidence to support this procedure, with most studies reported being case studies. *Anatomy:* Consists of several ganglia between the L1 and L5 vertebra. *Proposed Indications:* Circulatory insufficiency of the leg: (Arteriosclerotic disease; Claudication: Rest pain; Ischemic ulcers; Diabetic gangrene; Pain following arterial embolus). Pain: Herpes Zoster; Post-herpetic neuralgia; Frostbite; CRPS; Phantom pain. These blocks can be used diagnostically and therapeutically. *Adjunct therapy:* sympathetic therapy should be accompanied by aggressive physical therapy to optimize success. *Complications:* Back pain; Hematuria; Somatic block; Segmental nerve injury; Hypotension (secondary to vasodilation); Bleeding; Paralysis: Renal puncture/trauma. Genitofemoral neuralgia can occur with symptoms of burning dysesthesia in the anteromedial upper thigh. It is advised to not block at L4 to avoid this complication. *Adequacy of the block:* This should be determined, generally by measure of skin temperature (with an increase noted on the side of the block). Complete sympathetic blockade can be measured with the addition of tests of abolition of sweating and of the sympathogalvanic response. (Day, 2008) (Sayson, 2004) (Nader, 2005)

## **Return to work**

Recommended. Expedited return-to-work has been shown to be more useful in improving function and decreasing pain than extended disability. (Bernacki, 2000) (Boseman, 2001) (Colorado, 2002) (Melhorn, 2000) Lost productive time from common pain conditions among active workers costs an estimated 61.2 billion dollars per year. The majority (76.6%) of the lost productive time was explained by reduced performance while at work and not work absence. (Stewart, 2003) Chronic pain is independently related to low self-rated health in the general population. (Mantyselka-JAMA, 2003) Significant pain improvement is seen in groups that are prescribed light activity over groups that receive only medical treatment, especially in cases involving back pain. Extended bed rest is not recommended. (van Lankveld, 2000)

## **Rotta glucosamine sulfate**

See Glucosamine (and Chondroitin Sulfate).

## **RS-4i sequential stimulator**

See Transcutaneous electrotherapy.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## **RSD (reflex sympathetic dystrophy)**

Definition of this pain syndrome (not a procedure): New name for Reflex sympathetic dystrophy (RSD) is CRPS I. See Diagnostic Criteria for CRPS.

## **Salicylate topicals**

Recommended. Topical salicylate (e.g., Ben-Gay, methyl salicylate) is significantly better than placebo in chronic pain. (Mason-BMJ, 2004) See also Topical analgesics; & Topical analgesics, compounded.

## **Sclerotherapy (prolotherapy)**

Not recommended. Sclerotherapy/prolotherapy has no proven value via well-controlled, double blind studies and may have harmful effects. (Chronic Pain, 1998)

## **Serotonin norepinephrine reuptake inhibitors (SNRIs)**

See Duloxetine (Cymbalta®); & Milnacipran (Ixel®). See Antidepressants for chronic pain for general guidelines, as well as specific SNRI listing for more information and references.

## **Skelaxin® (metaxalone)**

Skelaxin® is a brand name for metaxalone marketed by King Pharmaceuticals. See Metaxalone (Skelaxin®).

## **SNRIs (serotonin noradrenaline reuptake inhibitors)**

Recommended as an option in first-line treatment of neuropathic pain, especially if tricyclics are ineffective, poorly tolerated, or contraindicated. See Antidepressants for chronic pain for general guidelines, as well as specific SNRI listing for more information and references. See also Venlafaxine (Effexor®) and Duloxetine (Cymbalta®).

## **Soma® (carisoprodol)**

See Carisoprodol (Soma®).

## **Spinal cord stimulators (SCS)**

Recommended only for selected patients in cases when less invasive procedures have failed or are contraindicated, for specific conditions indicated below, and following a successful temporary trial. Although there is limited evidence in favor of Spinal Cord Stimulators (SCS) for Failed Back Surgery Syndrome (FBSS) and Complex Regional Pain Syndrome (CRPS) Type I, more trials are needed to confirm whether SCS is an effective treatment for certain types of chronic pain. (Mailis-Gagnon-Cochrane, 2004) (BlueCross BlueShield, 2004) See indications list below. See Complete list of SCS\_References. This supporting evidence is significantly

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supplemented and enhanced when combined with the individually based observational evidence gained through an individual trial prior to implant. This individually based observational evidence should be used to demonstrate effectiveness and to determine appropriate subsequent treatment. (Sundaraj, 2005) Spinal Cord Stimulation is a treatment that has been used for more than 30 years, but only in the past five years has it met with widespread acceptance and recognition by the medical community. In the first decade after its introduction, SCS was extensively practiced and applied to a wide spectrum of pain diagnoses, probably indiscriminately. The results at follow-up were poor and the method soon fell in disrepute. In the last decade there has been growing awareness that SCS is a reasonably effective therapy for many patients suffering from neuropathic pain for which there is no alternative therapy. There are several reasons for this development, the principal one being that the indications have been more clearly identified. The enhanced design of electrodes, leads, and receivers/stimulators has substantially decreased the incidence of re-operations for device failure. Further, the introduction of the percutaneous electrode implantation has enabled trial stimulation, which is now commonly recognized as an indispensable step in assessing whether the treatment is appropriate for individual patients. (Furlan-Cochrane, 2004) These implantable devices have a very high initial cost relative to conventional medical management (CMM); however, over the lifetime of the carefully selected patient, SCS may lead to cost-saving and more health gain relative to CMM for FBSS and CRPS. (Taylor, 2005) (Taylor, 2006) SCS for treatment of chronic nonmalignant pain, including FBSS, has demonstrated a 74% long-term success rate (Kumar, 2006). SCS for treatment of failed back surgery syndrome (FBSS) reported better effectiveness compared to reoperation (North, 2005). A cost utility analysis of SCS versus reoperation for FBSS based on this RCT concluded that SCS was less expensive and more effective than reoperation, and should be the initial therapy of choice. Should SCS fail, reoperation is unlikely to succeed. (North, 2007) CRPS patients implanted with SCS reported pain relief of at least 50% over a median follow-up period of 33 months. (Taylor, 2006) SCS appears to be an effective therapy in the management of patients with CRPS. (Kemler, 2004) (Kemler, 2000) Recently published 5-year data from this study showed that change in pain intensity was not significantly different between the SCS plus PT group and the PT alone group, but in the subgroup analysis of implanted SCS patients, the change in pain intensity between the two groups approached statistical significance in favor of SCS, and 95% of patients with an implant would repeat the treatment for the same result. A thorough understanding of these results including the merits of intention-to-treat and as-treated forms of analysis as they relate to this therapy (where trial stimulation may result in a large drop-out rate) should be undertaken prior to definitive conclusions being made. (Kemler, 2008) Permanent pain relief in CRPS-I can be attained under long-term SCS therapy combined with physical therapy. (Harke, 2005) Neuromodulation may be successfully applied in the treatment of visceral pain, a common form of pain when internal organs are damaged or injured, if more traditional analgesic treatments have been unsuccessful. (Kapural, 2006) (Prager, 2007) A recent RCT of 100 failed back surgery syndrome patients randomized to receive spinal cord stimulation plus conventional medical management (SCS group) or conventional medical management alone (CMM group), found that 48% of SCS patients versus 9% of CMM patients achieved the primary outcome of 50% or more pain relief at 6 months. This study, funded by Medtronic, suggested that FBSS patients randomized to spinal cord stimulation had 9 times the odds of achieving the primary end point. (Kumar, 2007) According to the European Federation of Neurological Societies (EFNS), spinal cord stimulation (SCS) is efficacious in failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) type I (level B

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recommendation). (Cruccu, 2007) The National Institute for Health and Clinical Excellence (NICE) of the UK just completed their Final Appraisal Determination (FAD) of the medical evidence on spinal cord stimulation (SCS), concluding that SCS is recommended as a treatment option for adults with chronic neuropathic pain lasting at least 6 months despite appropriate conventional medical management, and who have had a successful trial of stimulation. Recommended conditions include failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS). (NICE, 2008)

## **Indications for stimulator implantation:**

- Failed back syndrome (persistent pain in patients who have undergone at least one previous back operation), more helpful for lower extremity than low back pain, although both stand to benefit, 40-60% success rate 5 years after surgery. It works best for neuropathic pain. Neurostimulation is generally considered to be ineffective in treating nociceptive pain. The procedure should be employed with more caution in the cervical region than in the thoracic or lumbar.
- Complex Regional Pain Syndrome (CRPS)/Reflex sympathetic dystrophy (RSD), 70-90% success rate, at 14 to 41 months after surgery. (Note: This is a controversial diagnosis.)
- Post amputation pain (phantom limb pain), 68% success rate
- Post herpetic neuralgia, 90% success rate
- Spinal cord injury dysesthesias (pain in lower extremities associated with spinal cord injury)
- Pain associated with multiple sclerosis
- Peripheral vascular disease (insufficient blood flow to the lower extremity, causing pain and placing it at risk for amputation), 80% success at avoiding the need for amputation when the initial implant trial was successful. The data is also very strong for angina. (Flotte, 2004)

## **Spinal cord stimulators, psychological evaluations**

See Psychological evaluations, SCS (spinal cord stimulators).

## **SSRIs (selective serotonin reuptake inhibitors)**

Not recommended as a treatment for chronic pain, but SSRIs may have a role in treating secondary depression. Selective serotonin reuptake inhibitors (SSRIs), a class of antidepressants that inhibit serotonin reuptake without action on noradrenaline, are controversial based on controlled trials. It has been suggested that the main role of SSRIs may be in addressing psychological symptoms associated with chronic pain. More information is needed regarding the role of SSRIs and pain. SSRIs have not been shown to be effective for low back pain. See Antidepressants for chronic pain for general guidelines, as well as specific SSRI listing for more information and references.

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## **Stellate ganglion block**

Recommendations are generally limited to diagnosis and therapy for CRPS. See CRPS, sympathetic and epidural blocks for specific recommendations for treatment. Detailed information about stellate ganglion blocks, thoracic sympathetic blocks, and lumbar sympathetic blocks is found in Regional sympathetic blocks.

## **Substance abuse (tolerance, dependence, addiction)**

The American Pain Society, American Academy of Pain Medicine, and American Society of Addiction Medicine have jointly defined the following (AAPM3, 2001):

1) Tolerance: “A state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug’s effects over time.” This is characterized by the need for higher doses of the medication to achieve the same pain effect and/or a diminished pain relief effect with continued use of the medication. In terms of opioids, most patients develop their plateau dose of opioids within about 2 months. (VA/DoD, 2003) One option to consider besides increasing the dose is to switch to another opioid.

2) Physical dependence: “A state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.” Abrupt cessation causes physiologic withdrawal. This can be expected with the use of opioids. This is not synonymous with addiction. Tolerance and withdrawal are 2 different conditions.

3) Addiction: “A primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations.”

### **DSM-IV Criteria for substance dependence (a more serious condition than substance abuse):**

1) Tolerance, 2) Withdrawal, 3) The substance is taken in amounts that are greater than intended or for a longer duration, 4) The patient is unable to cut down or quit the substance and/or desires to cut down or quit, 5) A great deal of time is spent obtaining the substance (for example, going to multiple doctors), and a great deal of time is spent in recovering from the effects of the substance, 6) Functioning is affected, including social, occupational and recreational activities, 7) The substance is causing physical or psychological problems and the patient is aware of this, but use is continued. (APA, 1994)

### **DSM-IV Criteria for substance abuse**

1) Failure to fulfill major role obligations at work, school or home, 2) Recurrent substance abuse in situations in which it is physically hazardous, 3) Recurrent legal

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problems associated with substance abuse, 4) Continued use despite persistent or recurrent social or interpersonal problems related to use.

## **Cautionary red flags for patients that may potentially abuse opioids:**

(a) History of alcohol or substance abuse, (b) Active alcohol or substance abuse, (c) Borderline personality disorder, (d) Mood disorders (depression) or psychotic disorders, (e) Non-return to work for >6 months, (f) Poor response to opioids in the past (Washington, 2002)

## **Cautionary red flags of addiction:**

1) Adverse consequences: (a) Decreased functioning, (b) Observed intoxication, (c) Negative affective state

2) Impaired control over medication use: (a) Failure to bring in unused medications, (b) Dose escalation without approval of the prescribing doctor, (c) Requests for early prescription refills, (d) Reports of lost or stolen prescriptions, (e) Unscheduled clinic appointments in “distress”, (f) Frequent visits to the ED, (g) Family reports of overuse or intoxication

3) Craving and preoccupation: (a) Non-compliance with other treatment modalities, (b) Failure to keep appointments, (c) No interest in rehabilitation, only in symptom control, (d) No relief of pain or improved function with opioid therapy, (e) Medications are provided by multiple providers. (Wisconsin, 2004)

## **Sympathectomy**

See CRPS, sympathectomy.

## **Sympathetic therapy**

See Transcutaneous electrotherapy.

## **Sympathetically independent pain (SIP)**

See Sympathetically maintained pain (SMP).

## **Sympathetically maintained pain (SMP)**

Definition: Sympathetically maintained pain (SMP) is pain that is maintained by sympathetic efferent innervation or by circulating catecholamines. (Stanton-Hicks, 1995) In more chronic stages, SMP may develop into sympathetically independent pain (SIP) or there may be mixed elements. (Ribbers, 2003) SMP and SIP may also be seen in almost any type of neuropathic pain disorder. Therefore, pain relief may be found after sympatholysis in multiple conditions in addition to CRPS, and may be a reflection of response to sympathetic activity found in other

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sympathetically maintained pain conditions. (Stanton-Hicks, 2004) See CRPS, diagnostic criteria; CRPS, medications; CRPS, sympathetic and epidural blocks; & Regional sympathetic blocks.

### **TENS, chronic pain (transcutaneous electrical nerve stimulation)**

See Transcutaneous electrotherapy.

### **TENS, post operative pain (transcutaneous electrical nerve stimulation)**

See Transcutaneous electrotherapy.

### **Testosterone replacement for hypogonadism (related to opioids)**

Recommended in limited circumstances for patients taking high-dose long-term opioids with documented low testosterone levels. Hypogonadism has been noted in patients receiving intrathecal opioids and long-term high dose opioids. Routine testing of testosterone levels in men taking opioids is not recommended; however, an endocrine evaluation and/or testosterone levels should be considered in men who are taking long term, high dose oral opioids or intrathecal opioids and who exhibit symptoms or signs of hypogonadism, such as gynecomastia. If needed, testosterone replacement should be done by a physician with special knowledge in this field given the potential side effects such as hepatomas. There are multiple delivery mechanisms for testosterone. Hypogonadism secondary to opiates appears to be central, although the exact mechanism has not been determined. The evidence on testosterone levels in long-term opioid users is not randomized or double-blinded, but there are studies that show that there is an increased incidence of hypogonadism in people taking opioids, either intrathecal or oral. There is also a body of literature showing that improvement in strength and other function in those who are testosterone deficient who receive replacement. (Nakazawa, 2006) (Page, 2005) (Rajagopal, 2004) This appears to be more pronounced than in patients taking oral opiates than in patients receiving intrathecal opioids, and this difference seems to be related to differences in absorption. Hypogonadism secondary to opiates appears to be central, although the exact mechanism has not been determined. (Abs, 2000) (Roberts, 2002) (Roberts, 2000) Etiology of decreased sexual function, a symptom of hypogonadism, is confounded by several factors including the following: (1) The role of chronic pain itself on sexual function; (2) The natural occurrence of decreased testosterone that occurs with aging; (3) The documented side effect of decreased sexual function that is common with other medications used to treat pain (SSRIs, tricyclic antidepressants, and certain anti-epilepsy drugs); & (4) The role of comorbid conditions such as diabetes, hypertension, and vascular disease in erectile dysfunction. There is little information in peer-reviewed literature as to how to treat opioid induced androgen deficiency.

*Long-term safety data of testosterone replacement (overall):* Not available.

*Cardiovascular risk:* There have been no large randomized controlled trials to evaluate the cardiovascular risk associated with long-term testosterone use, although current studies weakly support that there is no association with important cardiovascular effects. (Haddad 2007)

*Osteoporosis:* The extent to which testosterone can prevent and treat osteoporosis remains unclear. (Tracz 2006) (Isidori, 2005)

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*Sexual function:* Current trials of testosterone replacement in patients with documented low testosterone levels have shown a moderate nonsignificant and inconsistent effect of testosterone on erectile function, a large effect on libido, and no significant effect on overall sexual satisfaction. (Bolona, 2007) (Isidori, 2005)

The one study (sponsored by the drug company) that has evaluated the use of testosterone replacement in patients with opioid-induced androgen deficiency, measured morning serum free testosterone levels and PSA prior to replacement. This study did not include patients taking antidepressants. (Daniell, 2006)

## **THC (tetrahydrocannabinol)**

See Cannabinoids.

## **Tiagabine (Gabitril®)**

See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Tiagabine listing.

## **Tizanidine (Zanaflex®)**

Tizanidine is a muscle relaxant. See Muscle relaxants.

## **Topical Analgesics**

Recommended as an option as indicated below. Largely experimental in use with few randomized controlled trials to determine efficacy or safety. Primarily recommended for neuropathic pain when trials of antidepressants and anticonvulsants have failed. (Namaka, 2004) These agents are applied locally to painful areas with advantages that include lack of systemic side effects, absence of drug interactions, and no need to titrate. (Colombo, 2006) Many agents are compounded as monotherapy or in combination for pain control (including NSAIDs, opioids, capsaicin, local anesthetics, antidepressants, glutamate receptor antagonists,  $\alpha$ -adrenergic receptor agonist, adenosine, cannabinoids, cholinergic receptor agonists,  $\gamma$  agonists, prostanoids, bradykinin, adenosine triphosphate, biogenic amines, and nerve growth factor). (Argoff, 2006) There is little to no research to support the use of many of these agents. ***Any compounded product that contains at least one drug (or drug class) that is not recommended is not recommended.*** The use of these compounded agents requires knowledge of the specific analgesic effect of each agent and how it will be useful for the specific therapeutic goal required. [Note: Topical analgesics work locally underneath the skin where they are applied. These do not include transdermal analgesics that are systemic agents entering the body through a transdermal means. See Duragesic® (fentanyl transdermal system).]

***Non-steroidal antiinflammatory agents (NSAIDs):*** The efficacy in clinical trials for this treatment modality has been inconsistent and most studies are small and of short duration. Topical NSAIDs have been shown in meta-analysis to be superior to placebo during the first 2 weeks of treatment for osteoarthritis, but either not afterward, or with a diminishing effect over another 2-week period. (Lin, 2004) (Bjordal, 2007) (Mason, 2004) When investigated specifically for osteoarthritis of the knee, topical NSAIDs have been shown to be superior to placebo for 4 to 12 weeks. In this study the effect appeared to diminish over time and it was

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stated that further research was required to determine if results were similar for all preparations. (Biswal, 2006) These medications may be useful for chronic musculoskeletal pain, but there are no long-term studies of their effectiveness or safety. (Mason, 2004) *Indications: Osteoarthritis and tendinitis, in particular, that of the knee and elbow or other joints that are amenable to topical treatment:* Recommended for short-term use (4-12 weeks). There is little evidence to utilize topical NSAIDs for treatment of osteoarthritis of the spine, hip or shoulder. *Neuropathic pain:* Not recommended as there is no evidence to support use. *FDA-approved agents: Voltaren® Gel 1% (diclofenac):* Indicated for relief of osteoarthritis pain in joints that lend themselves to topical treatment (ankle, elbow, foot, hand, knee, and wrist). It has not been evaluated for treatment of the spine, hip or shoulder. Maximum dose should not exceed 32 g per day (8 g per joint per day in the upper extremity and 16 g per joint per day in the lower extremity). The most common adverse reactions were dermatitis and pruritus. (Voltaren® package insert) For additional adverse effects: See NSAIDs, GI symptoms and cardiovascular risk; & NSAIDs, hypertension and renal function. *Non FDA-approved agents: Ketoprofen:* This agent is not currently FDA approved for a topical application. It has an extremely high incidence of photocontact dermatitis. (Diaz, 2006) (Hindsen, 2006) Absorption of the drug depends on the base it is delivered in. (Gurol, 1996). Topical treatment can result in blood concentrations and systemic effect comparable to those from oral forms, and caution should be used for patients at risk, including those with renal failure. (Krummel 2000)

***Lidocaine Indication:*** *Neuropathic pain* Recommended for localized peripheral pain after there has been evidence of a trial of first-line therapy (tri-cyclic or SNRI anti-depressants or an AED such as gabapentin or Lyrica). Topical lidocaine, in the formulation of a dermal patch (Lidoderm<sup>®</sup>) has been designated for orphan status by the FDA for neuropathic pain. Lidoderm is also used off-label for diabetic neuropathy. No other commercially approved topical formulations of lidocaine (whether creams, lotions or gels) are indicated for neuropathic pain. Non-dermal patch formulations are generally indicated as local anesthetics and anti-pruritics. Further research is needed to recommend this treatment for chronic neuropathic pain disorders other than post-herpetic neuralgia. Formulations that do not involve a dermal-patch system are generally indicated as local anesthetics and anti-pruritics. In February 2007 the FDA notified consumers and healthcare professionals of the potential hazards of the use of topical lidocaine. Those at particular risk were individuals that applied large amounts of this substance over large areas, left the products on for long periods of time, or used the agent with occlusive dressings. Systemic exposure was highly variable among patients. Only FDA-approved products are currently recommended. (Argoff, 2006) (Dworkin, 2007) (Khaliq-Cochrane, 2007) (Knotkova, 2007) (Lexi-Comp, 2008) *Non-neuropathic pain:* Not recommended. There is only one trial that tested 4% lidocaine for treatment of chronic muscle pain. The results showed there was no superiority over placebo. (Scudts, 1995)

***Capsaicin:*** Recommended only as an option in patients who have not responded or are intolerant to other treatments. *Formulations:* Capsaicin is generally available as a 0.025% formulation (as a treatment for osteoarthritis) and a 0.075% formulation (primarily studied for post-herpetic neuralgia, diabetic neuropathy and post-mastectomy pain). There have been no studies of a 0.0375% formulation of capsaicin and there is no current indication that this increase over a 0.025% formulation would provide any further efficacy. *Indications:* There are positive randomized studies with capsaicin cream in patients with osteoarthritis, fibromyalgia, and

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chronic non-specific back pain, but it should be considered experimental in very high doses. Although topical capsaicin has moderate to poor efficacy, it may be particularly useful (alone or in conjunction with other modalities) in patients whose pain has not been controlled successfully with conventional therapy. The number needed to treat in musculoskeletal conditions was 8.1. The number needed to treat for neuropathic conditions was 5.7. (Robbins, 2000) (Keitel, 2001) (Mason-*BMJ*, 2004) See also Capsaicin.

**Baclofen:** Not recommended. There is currently one Phase III study of Baclofen-Amitriptyline-Ketamine gel in cancer patients for treatment of chemotherapy-induced peripheral neuropathy. There is no peer-reviewed literature to support the use of topical baclofen.

**Other muscle relaxants:** *There is no evidence for use of any other muscle relaxant as a topical product.*

**Gabapentin:** Not recommended. There is no peer-reviewed literature to support use.

**Other antiepilepsy drugs:** *There is no evidence for use of any other antiepilepsy drug as a topical product.*

**Ketamine:** Under study: Only recommended for treatment of neuropathic pain in refractory cases in which all primary and secondary treatment has been exhausted. Topical ketamine has only been studied for use in non-controlled studies for CRPS I and post-herpetic neuralgia and both have shown encouraging results. The exact mechanism of action remains undetermined. (Gammaitoni, 2000) (Lynch, 2005) See also Glucosamine (and Chondroitin Sulfate).

## Topical Analgesics, compounded

See Topical analgesics.

## Topical NSAIDs

See Non-steroidal antiinflammatory agents (NSAIDs) entry under Topical analgesics.

## Topiramate (Topamax®)

See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Topiramate listing.

## Tramadol (Ultram®)

Tramadol (Ultram®) is a centrally acting synthetic opioid analgesic and it is not recommended as a first-line oral analgesic. For more information and references, see Opioids. See also Opioids for neuropathic pain.

## Transcutaneous electrical nerve stimulation (TENS)

See Transcutaneous electrotherapy.

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## Transcutaneous electrotherapy

Electrotherapy represents the therapeutic use of electricity and is another modality that can be used in the treatment of pain. Transcutaneous electrotherapy is the most common form of electrotherapy where electrical stimulation is applied to the surface of the skin. The earliest devices were referred to as TENS (transcutaneous electrical nerve stimulation) and are the most commonly used. It should be noted that there is not one fixed electrical specification that is standard for TENS; rather there are several electrical specifications. Other devices (such as H-wave stimulation (devices), Interferential Current Stimulation, Microcurrent electrical stimulation (MENS devices), RS-4i sequential stimulator, Electroceutical Therapy (bioelectric nerve block), Neuromuscular electrical stimulation (NMES devices), Sympathetic therapy, Dynatron STS) have been designed and are distinguished from TENS based on their electrical specifications to be discussed in detail below. The following individual treatment topics are grouped together under the topic heading, “Transcutaneous Electrotherapy [DWC]” and are intended to allow the users of the chronic pain medical treatment guidelines to compare their benefits and to choose amongst the various transcutaneous electrical stimulation devices. All of the following individual treatment topics are from the ODG guidelines.

### **TENS, chronic pain (transcutaneous electrical nerve stimulation)**

Not recommended as a primary treatment modality, but a one-month home-based TENS trial may be considered as a noninvasive conservative option, if used as an adjunct to a program of evidence-based functional restoration, for the conditions described below. While TENS may reflect the long-standing accepted standard of care within many medical communities, the results of studies are inconclusive; the published trials do not provide information on the stimulation parameters which are most likely to provide optimum pain relief, nor do they answer questions about long-term effectiveness. (Carroll-Cochrane, 2001) Several published evidence-based assessments of transcutaneous electrical nerve stimulation (TENS) have found that evidence is lacking concerning effectiveness. One problem with current studies is that many only evaluated single-dose treatment, which may not reflect the use of this modality in a clinical setting. Other problems include statistical methodology, small sample size, influence of placebo effect, and difficulty comparing the different outcomes that were measured.

Recommendations by types of pain: A home-based treatment trial of one month may be appropriate for neuropathic pain and CRPS II (conditions that have limited published evidence for the use of TENS as noted below), and for CRPS I (with basically no literature to support use).

Neuropathic pain: Some evidence (Chong, 2003), including diabetic neuropathy (Spruce, 2002) and post-herpetic neuralgia. (Niv, 2005)

Phantom limb pain and CRPS II: Some evidence to support use. (Finsen, 1988) (Lundeberg, 1985)

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Spasticity: TENS may be a supplement to medical treatment in the management of spasticity in spinal cord injury. (Aydin, 2005)

Multiple sclerosis (MS): While TENS does not appear to be effective in reducing spasticity in MS patients it may be useful in treating MS patients with pain and muscle spasm. (Miller, 2007)

How it works: TENS consists of an electrical pulse generator connected to skin-surface electrodes that apply stimulation to peripheral nerves at well-tolerated frequencies. Electrodes can either be placed at the site of pain or other locations, using a trial and error methodology. A TENS unit can be varied by amplitude, pulse width (duration) and pulse rate (frequency). The most common applications include (1) high frequency or conventional TENS (40-150 Hz, with a short duration of up to 50 microseconds) and (2) low frequency or acupuncture-like TENS (1-4 Hz at a high stimulus intensity). Other modes of TENS include: (1) brief-intense TENS (>80 Hz); (2) burst TENS (bursts at less than 10 Hz) at high frequency; and (3) modulation TENS. The difference between clinical effectiveness of the modalities has not been well defined. (Koke, 2004)

Recent studies: There has been a recent meta-analysis published that came to a conclusion that there was a significant decrease in pain when electrical nerve stimulation (ENS) of most types was applied to any anatomic location of chronic musculoskeletal pain (back, knee, hip, neck) for any length of treatment. Of the 38 studies used in the analysis, 35 favored ENS over placebo. All locations of pain were included based on the rationale that “mechanism, rather than anatomic location of pain, is likely to be a critical factor for therapy.” The overall design of this study used questionable methodology and the results require further evaluation before application to specific clinical practice. (Johnson, 2007) (Novak, 2007) (Furlan, 2007)

Although electrotherapeutic modalities are frequently used in the management of CLBP, few studies were found to support their use. Most studies on TENS can be considered of relatively poor methodological quality. TENS does not appear to have an impact on perceived disability or long-term pain. Highfrequency TENS appears to be more effective on pain intensity when compared with low frequency, but this has to be confirmed in future comparative trials. It is also not known if adding TENS to an evidence-based intervention, such as exercise, improves even more outcomes, but studies assessing the interactions between exercise and TENS found no cumulative impact. (Poitras, 2008)

### Current Treatment Coverage Guidelines:

- BlueCross BlueShield: TENS is considered investigational for treatment of chronic back pain, chronic pain and post-surgical pain, but is covered for certain members based on CMS rules. (BlueCross BlueShield, 2007)
- CMS: The use of TENS for the relief of acute post-operative pain is covered for 30 days or less (as an adjunct and/or alternative to pharmaceutical treatment). TENS is also covered as treatment for chronic intractable pain. Medicare

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

requires a month-long trial period in order to determine if there is a significant therapeutic effect. (Medicare, 2006)

- Aetna & Humana: consistent with the CMS Guidelines (Aetna, 2005) (Humana, 2004)
- VA: TENS is considered equivocal when compared to other modalities. (US Dept VA, 2001)
- European Federation of Neurological Societies (EFNS): TENS may be better than placebo (level C) although worse than electro-acupuncture (level B); TENS is non-invasive and suitable as a preliminary or add-on therapy. (Crucchi, 2007)

### Criteria for the use of TENS:

*Chronic intractable pain* (for the conditions noted above):

- Documentation of pain of at least three months duration
- There is evidence that other appropriate pain modalities have been tried (including medication) and failed
- A one-month trial period of the TENS unit should be documented (as an adjunct to ongoing treatment modalities within a functional restoration approach) with documentation of how often the unit was used, as well as outcomes in terms of pain relief and function; rental would be preferred over purchase during this trial
- Other ongoing pain treatment should also be documented during the trial period including medication usage
- A treatment plan including the specific short- and long-term goals of treatment with the TENS unit should be submitted
- A 2-lead unit is generally recommended; if a 4-lead unit is recommended, there must be documentation of why this is necessary

*Form-fitting TENS device*: This is only considered medically necessary when there is documentation that there is such a large area that requires stimulation that a conventional system cannot accommodate the treatment, that the patient has medical conditions (such as skin pathology) that prevents the use of the traditional system, or the TENS unit is to be used under a cast (as in treatment for disuse atrophy)

### TENS, post operative pain (transcutaneous electrical nerve stimulation)

Recommended as a treatment option for acute post-operative pain in the first 30 days post-surgery. Transcutaneous electrical nerve stimulation (TENS) appears to be most effective for mild to moderate thoracotomy pain. (Solak, 2007) (Erdogan, 2005). It has been shown to be of lesser effect, or not at all for other orthopedic surgical procedures. (Breit, 2004) (Rosenquist 2003) The proposed necessity of the unit should be

## **CHRONIC PAIN MEDICAL TREATMENT GUIDELINES**

documented upon request. Rental would be preferred over purchase during this 30-day period.

### **Dynatron STS**

See Sympathetic therapy.

### **Electroceutical Therapy (bioelectric nerve block)**

Not recommended. Electroceutical therapy (also known as bioelectric nerve block) is experimental and investigational for the treatment of chronic pain (e.g., back pain, diabetic pain, joint pain, fibromyalgia, headache, and CRPS) because there is a lack of scientific evidence regarding the effectiveness of this technology. In addition, electroceutical treatments use much higher electrical frequencies than TENS units and may only be prescribed and administered under the supervision of a healthcare provider experienced in this method of treatment. (Aetna, 2005)

### **Galvanic Stimulation**

Not recommended. Considered investigational for all indications. Galvanic stimulation is characterized by high voltage, pulsed stimulation and is used primarily for local edema reduction through muscle pumping and polarity effect. Edema is comprised of negatively charged plasma proteins, which leak into the interstitial space. The theory of galvanic stimulation is that by placing a negative electrode over the edematous site and a positive electrode at a distant site, the monophasic high voltage stimulus applies an electrical potential which disperses the negatively charged proteins away from the edematous site, thereby helping to reduce edema. (BlueCrossBlueShield, 2005)

### **H-wave stimulation (HWT)**

Not recommended as an isolated intervention, but a one-month home-based trial of H-Wave stimulation may be considered as a noninvasive conservative option for diabetic neuropathic pain (Julka, 1998) (Kumar, 1997) (Kumar, 1998), or chronic soft tissue inflammation if used as an adjunct to a program of evidence-based functional restoration, and only following failure of initially recommended conservative care, including recommended physical therapy (i.e., exercise) and medications, plus transcutaneous electrical nerve stimulation (TENS). In a recent retrospective study suggesting effectiveness of the H-wave device, the patient selection criteria included a physician-documented diagnosis of chronic soft-tissue injury or neuropathic pain in an upper or lower extremity or the spine that was unresponsive to conventional therapy, including physical therapy, medications, and TENS. (Blum, 2006) (Blum2, 2006) There is no evidence that H-Wave is more effective as an initial treatment when compared to TENS for analgesic effects. A randomized controlled trial comparing analgesic effects of H-wave therapy and TENS on pain threshold found that there were no differences between the different modalities or HWT frequencies. (McDowell2, 1999) [Note: This may be a different device than the H-Wave approved for use in the US.] Regarding tissue repair,

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another study suggests that low-frequency HWT may produce direct localized effects on cutaneous blood flow, a finding relevant for clinicians working in the field of tissue repair. (McDowell, 1999) The one-month HWT trial may be appropriate to permit the physician and provider licensed to provide physical therapy to study the effects and benefits, and it should be documented (as an adjunct to ongoing treatment modalities within a functional restoration approach) as to how often the unit was used, as well as outcomes in terms of pain relief and function. Rental would be preferred over purchase during this trial. Trial periods of more than one month should be justified by documentation submitted for review. While H-Wave and other similar type devices can be useful for pain management, they are most successfully used as a tool in combination with functional improvement. H-wave stimulation is a form of electrical stimulation that differs from other forms of electrical stimulation, such as transcutaneous electrical nerve stimulation (TENS), in terms of its waveform. While physiatrists, chiropractors, or podiatrists may perform H-wave stimulation, H-wave devices are also available for home use. H-wave stimulation is sometimes used for the treatment of pain related to a variety of etiologies, muscle sprains, temporomandibular joint dysfunctions or reflex sympathetic dystrophy. In fact, H-wave is used more often for muscle spasm and acute pain as opposed to neuropathy or radicular pain, since there is anecdotal evidence that H-Wave stimulation helps to relax the muscles, but there are no published studies to support this use, so it is not recommended at this time. H-wave stimulation has also been used to accelerate healing of wounds, such as diabetic ulcers. H-wave electrical stimulation must be distinguished from the H-waves that are a component of electromyography. (BlueCross BlueShield, 2007) (Aetna, 2005)

*Recent studies:* A recent low quality meta-analysis concluded that the findings indicate a moderate to strong effect of the H-Wave device in providing pain relief, reducing the requirement for pain medication and increasing functionality, with the most robust effect observed for improved functionality, suggesting that the H-Wave device may facilitate a quicker return to work and other related daily activities. The low quality rating for this “meta-analysis” is primarily because the numbers were dominated by results from studies that were not prospective randomized controlled trials, but instead were retrospective observational studies using a patient survey, the H-Wave Customer Service Questionnaire, without a prospective control group. More definitive results may be on the way. According to this study, "double-blinded studies of the H-Wave device are currently underway and results will be awaited with interest." (Blum, 2008)

### **Interferential Current Stimulation (ICS)**

Not recommended as an isolated intervention. There is no quality evidence of effectiveness except in conjunction with recommended treatments, including return to work, exercise and medications, and limited evidence of improvement on those recommended treatments alone. The randomized trials that have evaluated the effectiveness of this treatment have included studies for back pain, jaw pain, soft tissue shoulder pain, cervical neck pain and post-operative knee pain. (Van der Heijden, 1999) (Werner, 1999) (Hurley, 2001) (Hou, 2002) (Jarit, 2003) (Hurley, 2004) (CTAF, 2005) (Burch, 2008) The findings from these trials were either negative or non-interpretable for recommendation due to poor study design and/or methodologic issues. In addition,

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although proposed for treatment in general for soft tissue injury or for enhancing wound or fracture healing, there is insufficient literature to support Interferential current stimulation for treatment of these conditions. There are no standardized protocols for the use of interferential therapy; and the therapy may vary according to the frequency of stimulation, the pulse duration, treatment time, and electrode-placement technique. Two recent randomized double-blind controlled trials suggested that ICS and horizontal therapy (HT) were effective in alleviating pain and disability in patients with chronic low back pain compared to placebo at 14 weeks, but not at 2 weeks. The placebo effect was remarkable at the beginning of the treatment but it tended to vanish within a couple of weeks. The studies suggested that their main limitation was the heterogeneity of the low back pain subjects, with the interventions performing much better for back pain due to previous multiple vertebral osteoporotic fractures, and further studies are necessary to determine effectiveness in low back pain from other causes. (Zambito, 2006) (Zambito, 2007) A recent industry-sponsored study in the Knee Chapter concluded that interferential current therapy plus patterned muscle stimulation (using the RS-4i Stimulator) has the potential to be a more effective treatment modality than conventional low-current TENS for osteoarthritis of the knee. (Burch, 2008) This recent RCT found that either electroacupuncture or interferential electrotherapy, in combination with shoulder exercises, is equally effective in treating frozen shoulder patients. It should be noted that this study only showed the combined treatment effects with exercise as compared to no treatment, so the entire positive effect could have been due to the use of exercise alone. (Cheing, 2008) See also Sympathetic therapy. See also TENS, chronic pain.

*How it works:* Paired electrodes of two independent circuits carry differing medium-frequency alternating currents so that current flowing between each pair intersects at the underlying target. The frequency allows the Interferential wave to meet low impedance when crossing the skin. Treatments involve the use of two pairs of electrodes and most units allow variation in waveform, stimulus frequency and amplitude or intensity, and the currents rise and fall at different frequencies. It is theorized that the low frequency of the interferential current causes inhibition or habituation of the nervous system, which results in muscle relaxation, suppression of pain and acceleration of healing.

*How it is different than TENS:* It has been postulated that Interferential stimulation allows for deeper penetration of tissue, whereas TENS is predominantly a cutaneous or superficial stimulus. Interferential current is proposed to produce less impedance in the tissue and the intensity provided is suggested to be perceived as more comfortable. Because there is minimal skin resistance with the interferential current therapy, a maximum amount of energy goes deeper into the tissue. It also crisscrosses, as opposed to the linear application of the TENS. This crisscrossing is postulated to be more effective because it serves to confuse the nerve endings, preventing the treated area from adjusting to the current. There are no published randomized trials comparing TENS to Interferential current stimulation.

*Current US treatment coverage recommendations:* Health plans have taken a variety of positions with respect to ICS. *California Technology Assessment Forum* concluded that

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the treatment does not meet their criteria for coverage. (CTAF, 2005) *Aetna* considers it experimental because its effectiveness has not been established. (Aetna, 2007) *United Healthcare* concluded that clinical evidence supports its use for treatment of pain or non-surgical soft tissue injuries. (United, 2007) *Humana* provides coverage for acute postoperative or post-traumatic pain, or chronic pain of at least three months duration that is not responsive to other methods of pain management. (Humana, 2008) There is considerable variance in the *BlueCross BlueShield* coverage recommendations, and some BC/BS licensees reference ICS as investigational/not medically necessary (BlueCross BlueShield, 2006), but others do cover it. (BC/BS\_TN, 2008) *CMS* does not directly address its use. In workers' comp, Washington L&I covers these devices, but only from a single TENS supplier. (Washington, 2008) [Note: Coverage determinations by health insurance plans are not considered high quality evidence in formulating ODG recommendations, but may be provided for reference when high quality studies are not available.]

### **While not recommended as an isolated intervention, Patient selection criteria if Interferential stimulation is to be used anyway:**

Possibly appropriate for the following conditions if it has documented and proven to be effective as directed or applied by the physician or a provider licensed to provide physical medicine:

- Pain is ineffectively controlled due to diminished effectiveness of medications; or
- Pain is ineffectively controlled with medications due to side effects; or
- History of substance abuse; or
- Significant pain from postoperative conditions limits the ability to perform exercise programs/physical therapy treatment; or
- Unresponsive to conservative measures (e.g., repositioning, heat/ice, etc.).

If those criteria are met, then a one-month trial may be appropriate to permit the physician and physical medicine provider to study the effects and benefits. There should be evidence of increased functional improvement, less reported pain and evidence of medication reduction. A "jacket" should not be certified until after the one-month trial and only with documentation that the individual cannot apply the stimulation pads alone or with the help of another available person.

### **Microcurrent electrical stimulation (MENS devices)**

Not recommended. Based on the available evidence conclusions cannot be made concerning the effect of Microcurrent Stimulation Devices (MENS) on pain management and objective health outcomes. MENS is characterized by sub-sensory current that acts on the body's naturally occurring electrical impulses to decrease pain and facilitate the healing process. MENS differs from TENS in that it uses a significantly reduced electrical stimulation. TENS blocks pain, while MENS acts on the naturally occurring electrical impulses to decrease pain by stimulating the healing process. (BlueCross BlueShield, 2005)

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Neuromuscular electrical stimulation (NMES devices)

Not recommended. NMES is used primarily as part of a rehabilitation program following stroke and there is no evidence to support its use in chronic pain. There are no intervention trials suggesting benefit from NMES for chronic pain. (Moore, 1997) (Gaines, 2004) The scientific evidence related to electromyography (EMG)-triggered electrical stimulation therapy continues to evolve, and this therapy appears to be useful in a supervised physical therapy setting to rehabilitate atrophied upper extremity muscles following stroke and as part of a comprehensive PT program. Neuromuscular Electrical Stimulation Devices (NMES), NMES, through multiple channels, attempts to stimulate motor nerves and alternately causes contraction and relaxation of muscles, unlike a TENS device which is intended to alter the perception of pain. NMES devices are used to prevent or retard disuse atrophy, relax muscle spasm, increase blood circulation, maintain or increase range-of-motion, and re-educate muscles. Functional neuromuscular stimulation (also called electrical neuromuscular stimulation and EMG-triggered neuromuscular stimulation) attempts to replace stimuli from destroyed nerve pathways with computer-controlled sequential electrical stimulation of muscles to enable spinal-cord-injured or stroke patients to function independently, or at least maintain healthy muscle tone and strength. Also used to stimulate quadriceps muscles following major knee surgeries to maintain and enhance strength during rehabilitation. (BlueCross BlueShield, 2005) (Aetna, 2005)

## RS-4i sequential stimulator

See Interferential current stimulation (ICS).

## Sympathetic therapy

Not recommended. Sympathetic therapy is considered investigational. The lack of published outcomes from well-designed clinical trials prohibits scientific conclusions concerning the health outcome effects of sympathetic therapy for the treatment of pain. Sympathetic therapy describes a type of electrical stimulation of the peripheral nerves that is designed to stimulate the sympathetic nervous system in an effort to "normalize" the autonomic nervous system and alleviate chronic pain. Unlike TENS (transcutaneous electrical nerve stimulation) or interferential electrical stimulation, sympathetic therapy is not designed to treat local pain, but is designed to induce a systemic effect on sympathetically induced pain. The Dynatron STS device and a companion home device, Dynatron STS Rx, are devices that deliver sympathetic therapy. These devices received U.S. Food and Drug Administration (FDA) clearance in March 2001 through a 510(k) process. The FDA-labeled indication is as follows: "Electrical stimulation delivered by the Dynatron STS and Dynatron STS Rx is indicated for providing symptomatic relief of chronic intractable pain and/or management of post-traumatic or post-surgical pain." (Werners, 1999) (Washington, 2002) (BlueCross Blue-shield, 2005) (Aetna, 2005) See also Interferential therapy (ICS).

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Treatment for CRPS

See CRPS, treatment.

## Tricyclics

Recommended. Tricyclics are generally considered a first-line agent unless they are ineffective, poorly tolerated, or contraindicated. Analgesia generally occurs within a few days to a week, whereas antidepressant effect takes longer to occur. For peripheral neuropathic pain the NNT for tricyclics is 2.3, versus SSRIs of 6.8 and SNRIs of 4.6. See Antidepressants for chronic pain for general guidelines, as well as specific Tricyclics listing for more information and references.

## Trigger point injections

Recommended only for myofascial pain syndrome as indicated below, with limited lasting value. Not recommended for radicular pain. Trigger point injections with an anesthetic such as bupivacaine are recommended for non-resolving trigger points, but the addition of a corticosteroid is not generally recommended. Not recommended for radicular pain. A trigger point is a discrete focal tenderness located in a palpable taut band of skeletal muscle, which produces a local twitch in response to stimulus to the band. Trigger points may be present in up to 33-50% of the adult population. Myofascial pain syndrome is a regional painful muscle condition with a direct relationship between a specific trigger point and its associated pain region. These injections may occasionally be necessary to maintain function in those with myofascial problems when myofascial trigger points are present on examination. Not recommended for typical back pain or neck pain. (Graff-Radford, 2004) (Nelemans-Cochrane, 2002) For fibromyalgia syndrome, trigger point injections have not been proven effective. (Goldenberg, 2004)

### Criteria for the use of Trigger point injections:

Trigger point injections with a local anesthetic may be recommended for the treatment of chronic low back or neck pain with myofascial pain syndrome when all of the following criteria are met: (1) Documentation of circumscribed trigger points with evidence upon palpation of a twitch response as well as referred pain; (2) Symptoms have persisted for more than three months; (3) Medical management therapies such as ongoing stretching exercises, physical therapy, NSAIDs and muscle relaxants have failed to control pain; (4) Radiculopathy is not present (by exam, imaging, or neuro-testing); (5) Not more than 3-4 injections per session; (6) No repeat injections unless a greater than 50% pain relief is obtained for six weeks after an injection and there is documented evidence of functional improvement; (7) Frequency should not be at an interval less than two months; (8) Trigger point injections with any substance (e.g., saline or glucose) other than local anesthetic with or without steroid are not recommended. (Colorado, 2002) (BlueCross BlueShield, 2004)

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## **Tumor necrosis factor (TNF) modifiers**

Not recommended. Note: This drug was recently included in a list of 20 medications identified by the FDA's Adverse Event Reporting System, that are under FDA investigation. (FDA, 2008)

## **Turmeric**

See Curcumin (Turmeric).

## **Ultram® (tramadol)**

Ultram® is a brand of tramadol supplied by Ortho-McNeil Pharmaceutical. See Tramadol (Ultram®).

## **Ultrasound, therapeutic**

Not recommended. Therapeutic ultrasound is one of the most widely and frequently used electrophysical agents. Despite over 60 years of clinical use, the effectiveness of ultrasound for treating people with pain, musculoskeletal injuries, and soft tissue lesions remains questionable. There is little evidence that active therapeutic ultrasound is more effective than placebo ultrasound for treating people with pain or a range of musculoskeletal injuries or for promoting soft tissue healing. (Robertson, 2001)

## **Uncaria Tomentosa (Cat's Claw) [DWC]**

Uncaria Tomentosa (Cat's Claw) is not recommended for chronic pain.

## **Venlafaxine (Effexor®)**

Recommended as an option in first-line treatment of neuropathic pain. Venlafaxine (Effexor®) is a member of the selective-serotonin and norepinephrine reuptake inhibitor (SNRIs) class of antidepressants. It has FDA approval for treatment of depression and anxiety disorders. It is off-label recommended for treatment of neuropathic pain, diabetic neuropathy, fibromyalgia, and headaches. The initial dose is generally 37.5 to 75 mg/day with a usual increase to a dose of 75 mg b.i.d or 150 mg/day of the ER formula. The maximum dose of the immediate release formulation is 375 mg/day and of the ER formula is 225 mg/day. It may have an advantage over tricyclic antidepressants due to lack of anticholinergic side effects. Dosage requirements are necessary in patients with hepatic and renal impairment. (Namaka, 2004) See also Antidepressants for chronic pain for general guidelines, as well as specific Venlafaxine listing for more information and references.

## **Vicodin®**

See Opioids.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Vioxx® (rofecoxib)

Not recommended. *Note: Pulled from market 10/5/04.* See Anti-inflammatory medications and NSAIDs (non-steroidal anti-inflammatory drugs). Recent studies have shown an increase in the risk of myocardial infarction for rofecoxib (Vioxx), compared to NSAID's with an antiplatelet effect. (Choi, 2004) (Solomon, 2004)

## Weaning of Medications

Recommended as indicated below. *Opioids:* For opioids a slow taper is recommended. The longer the patient has taken opioids, the more difficult they are to taper. The process is more complicated with medical comorbidity, older age, female gender, and the use of multiple agents. Gradual weaning is recommended for long-term opioid users because opioids cannot be abruptly discontinued without probable risk of withdrawal symptoms. (Benzon, 2005) Patients with complex conditions with multiple comorbidities (including psych disorders) should be referred to an addiction medicine/psychiatry specialist. Opioid weaning should include the following: (a) Start with a complete evaluation of treatment, comorbidity, psychological condition; (b) Clear written instructions should be given to the patient and family; (c) If the patient can not tolerate the taper, refer to an expert (pain specialist, substance abuse specialist); (d) Taper by 20 to 50% per week of original dose for patients who are not addicted (the patient needs 20% of the previous day's dose to prevent withdrawal); (e) A slower suggested taper is 10% every 2 to 4 weeks, slowing to a reductions of 5% once a dose of 1/3 of the initial dose is reached; (f) Greater success may occur when the patient is switched to longer-acting opioids and then tapered; (g) Office visits should occur on a weekly basis; (h) Assess for withdrawal using a scale such as the Subjective Opioid Withdrawal Scale (SOWS) and Objective Opioid Withdrawal Scale (OOWS); & (i) Recognize that this may take months. *Benzodiazepine:* Tapering is required if used for greater than 2 weeks. (Benzon, 2005) (Ashton, 2005) (Kahan, 2006) This is more dangerous than opioid withdrawal, and takes more time, with the following recommendations: (1) The recommended rate of tapering is about 1/8 to 1/10 of the daily dose every 1 to 2 weeks; (2) Rate of withdrawal should be individually tapered; (3) Tapering may take as long as a year; (4) High-dose abusers or those with polydrug abuse may need in-patient detoxification; & (5) Withdrawal can occur when a chronic user switches to a benzodiazepine with a different receptor activity. (Lee, 2002) *Carisoprodol (Soma®):* This medication is metabolized to meprobamate, a barbiturate. At the highest levels of barbiturate tolerance, the patient is at risk of delirium, seizures or even death with abrupt discontinuation. There is little research in terms of weaning of high dose carisoprodol and there is no standard treatment regimen for patients with known dependence. Most treatment includes treatment for symptomatic complaints of withdrawal. Another option is to switch to phenobarbital to prevent withdrawal with subsequent tapering. A maximum dose of phenobarbital is 500 mg/day and the taper is 30 mg/day with a slower taper in an outpatient setting. Tapering should be individualized for each patient. (Boothby, 2003) (Heacock, 2004) (Washington, 2002) See also Detoxification; & Rapid detox.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

## Wellbutrin® (bupropion)

Wellbutrin® is the brand name for bupropion, an atypical antidepressant that acts as a norepinephrine and dopamine reuptake inhibitor, and is supplied by GlaxoSmithKline. See Bupropion (Wellbutrin®).

## White willow bark [DWC]

White willow bark is not recommended for chronic pain.

## Work conditioning, work hardening

Recommended as an option, depending on the availability of quality programs.

### **Criteria for admission to a Work Hardening Program:**

- (1) Work related musculoskeletal condition with functional limitations precluding ability to safely achieve current job demands, which are in the medium or higher demand level (i.e., not clerical/sedentary work). An FCE may be required showing consistent results with maximal effort, demonstrating capacities below an employer verified physical demands analysis (PDA).
- (2) After treatment with an adequate trial of physical or occupational therapy with improvement followed by plateau, but not likely to benefit from continued physical or occupational therapy, or general conditioning.
- (3) Not a candidate where surgery or other treatments would clearly be warranted to improve function.
- (4) Physical and medical recovery sufficient to allow for progressive reactivation and participation for a minimum of 4 hours a day for three to five days a week.
- (5) A defined return to work goal agreed to by the employer & employee:
  - (a) A documented specific job to return to with job demands that exceed abilities, OR
  - (b) Documented on-the-job training
- (6) The worker must be able to benefit from the program (functional and psychological limitations that are likely to improve with the program). Approval of these programs should require a screening process that includes file review, interview and testing to determine likelihood of success in the program.
- (7) The worker must be no more than 2 years past date of injury. Workers that have not returned to work by two years post injury may not benefit.
- (8) Program timelines: Work Hardening Programs should be completed in 4 weeks consecutively or less.
- (9) Treatment is not supported for longer than 1-2 weeks without evidence of patient compliance and demonstrated significant gains as documented by subjective and objective gains and measurable improvement in functional abilities.
- (10) Upon completion of a rehabilitation program (e.g. work hardening, work conditioning, outpatient medical rehabilitation) neither re-enrollment in nor repetition of the same or similar rehabilitation program is medically warranted for the same condition or injury.

### **ODG Physical Medicine Guidelines – Work Conditioning**

10 visits over 8 weeks

See also Physical medicine for general guidelines.

# CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

And, as with all physical medicine programs, Work Conditioning participation does not preclude concurrently being at work.

## Yoga

Recommended as an option only for select, highly motivated patients. There is considerable evidence of efficacy for mind-body therapies such as yoga in the treatment of chronic pain. Also, the impact on depression and disability could be considered as important outcomes for further study. Since outcomes from this therapy are very dependent on a highly motivated patient, we recommend approval where requested by a specific patient, but not adoption for use by any patient. (Astin, 2003) (Barrows, 2002) (Galantino, 2004)

## Ziconotide (Prialt®)

Recommended for use after there is evidence of a failure of a trial of intrathecal morphine or hydromorphone (Dilaudid), and only in individuals for whom the potential benefits outweigh the risks of serious neuropsychiatric adverse effects. The 2007 Polyanalgesic Consensus Conference Recommendations for the Management of Pain by Intrathecal Drug Delivery concluded that ziconotide should be updated to a first-line intrathecal drug.

Ziconotide (Prialt®) is a synthetic calcium channel blocker that is delivered intrathecally, offering a non-opioid option for treatment of chronic pain, and possibly, spasticity associated with spinal cord trauma. It is FDA-approved for the management of severe chronic pain in patients for whom intrathecal therapy is warranted and who are intolerant of other treatments, such as systemic analgesics, adjunctive therapies. This medication is meant to be an option for patients who are intolerant and/or refractory to intrathecal morphine. The advantage of the medication is that it is considered non-addictive. Current case reports have described many challenges in converting from morphine to ziconotide, including inadequate analgesia, adverse medication effects, and opioid withdrawal symptoms. An option for treatment is combining ziconotide with other currently available intrathecal medications, although this has not been studied in placebo-controlled trials.

*Adverse effects:* Prialt has been associated with severe CNS-related adverse effects, and a “black-box” warning has been issued in this regard. Neurological warnings include hallucinations, paranoid ideation, hostility, delirium, psychosis, manic reactions and decreased alertness. Certain patients may be at increased risk for psychiatric side effects including those with pre-existing history of depression with risk of suicide and patients with pre-existing psychosis. Cognitive impairment was noted in approximately 30% of patients in clinical trials, and this symptom was found to be reversible within about two weeks of discontinuation. Prialt is contraindicated in patients with a pre-existing history of psychosis. Prialt can be discontinued abruptly without evidence of withdrawal effects in the presence of serious adverse events.

*Dosage requirements:* The current recommendations suggested by the manufacturer for this medication include a low initial infusion rate (0.1 mcg/hour for a total of 2.4 mcg/day) and limiting infusion increases to 2-3 times a week. Current drug trials have evaluated the efficacy of

## CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

the medication for a 3-week duration only, but preliminary trials suggested that analgesic efficacy would be maintained long-term in open label trials.

*Post-marketing dose recommendations:* Post-marketing, an expert consensus-panel recommended a starting dose of 0.5 mcg/24 hours with upward titration of no more than 0.5 mcg/week due to increased risk of adverse effects with higher doses. (Fisher, 2005)

*Filling intervals:* The reservoir should be refilled initially at 14 days and at 40-day intervals thereafter if the drug is diluted (60 days if undiluted).

*Other precautions:* This medication is associated with elevation of serum creatinine kinase, with risk factors including male gender and concomitant use of anti-depressants, anti-convulsants and intrathecal morphine. This lab value should be monitored at least bi-weekly for the first month and at monthly intervals thereafter. Symptoms of myalgia include myasthenia, muscle cramps and unusual fatigue. (Thompson, 2006) (Wermeling 2005) (Lyseng-Williamson, 2006) (Lynch, 2006) (Rauck, 2006) (Deer, 2007) See Intrathecal drug delivery systems, medications.

### **Zonisamide (Zonegran®)**

See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Zonisamide listing.