MEDICAL TREATMENT UTILIZATION SCHEDULE (MTUS)
CHRONIC PAIN MEDICAL TREATMENT GUIDELINES

Part 1: Introduction

Part 2: Official Disability Guidelines (ODG) Treatment in Workers' Compensation — Pain (Chronic)

July 28, 2016

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This Chapter of the Medical Treatment Utilization Schedule is adopted from *Official Disability Guidelines* (ODG) Treatment in Workers' Comp, published and copyrighted by the Work Loss Data Institute.

Any links to treatment guidelines external to this document refer to the Medical Treatment Utilization Schedule.

PART 1: Introduction

These Chronic Pain Medical Treatment Guidelines apply when a patient has pain that persists three (3) or more months from the initial onset of pain (i.e.,12 weeks or more) as determined by following the relevant sections of the Medical Treatment Utilization Schedule (MTUS). In following the Clinical Topics section of the MTUS (8 CCR § 9792.23), the physician begins by assessing the presenting complaint and determining whether there is a "red flag for a potentially serious condition" that would trigger an immediate intervention. Upon ruling out a potentially serious condition, the physician should provide conservative management, that is, a treatment approach designed to avoid surgical and other medical and therapeutic measures with higher risk of harm compared to benefit.(Singh, 2013). If the complaint persists, the physician needs to reconsider the diagnosis and decide whether a specialist evaluation is necessary. The Chronic Pain Medical Treatment Guidelines provide 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 an introduction (Part 1) and specific information on interventions and treatments for chronic pain (Part 2), a reformatted version of evidence-based treatment guidelines from the April 6, 2015 version of the Work Loss Data Institute's Official Disability Guidelines (ODG) Treatment in Workers' Compensation – Pain (Chronic), adapted with permission from the publisher. For specific guidance on opioid use, refer to the "MTUS Opioids Treatment Guidelines."

Definitions:

Pain: The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage." (Merskey, 1994) This definition describes pain as a subjective experience; therefore, unlike hypertension or diabetes, there is no objective measurement for pain. Analysis of the objective data (history, psychosocial assessment, physical findings, imaging results, lab tests, etc.) is needed to evaluate the patient's subjective report of pain.

Types of Pain (Acute vs Chronic): Pain comes in many forms. Understanding which kind or kinds of pain a person is experiencing is a first step toward treatment. Although acute and chronic pain is considered separately below, an individual can experience them simultaneously. Furthermore, current research shows that pain exists more on a continuum than in discrete categories of "acute" or "chronic" pain. This means that, for some patients, the mechanisms responsible for pain persistence are engaged early in the injury process. Therefore, it is important to identify persons at risk for the development of chronic pain and to establish preventative measures to reduce the likelihood of pain persistence.

- *Acute pain*, by definition, is of sudden onset and expected to be of short duration. It can usually be linked to a specific event, injury, or illness—a muscle strain, a bone fracture, severe sunburn, or a kidney stone, for example. People can self-manage many types of acute pain with over-the-counter medications or a short course of stronger analgesics and rest. Acute pain usually subsides when the underlying cause resolves, such as when a fracture heals, or kidney stone or diseased tooth is removed. In the "MTUS Opioids Treatment Guidelines," acute pain is defined as pain lasting up to one month and subacute pain as pain last between one and three months.

- *Chronic pain* is any pain that lasts three (3) or more months from the initial onset of pain (i.e., over 12 weeks) and can be frustratingly difficult to treat. In the "MTUS Opioids Treatment Guidelines," chronic pain is also defined as pain lasting three (3) or more months from the initial onset of pain.

Types of Pain (Mechanisms): Pain mechanisms can be broadly categorized as nociceptive, inflammatory, neuropathic, or unknown.

- *Nociceptive pain*: 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." (Smith, 2009) Nociceptive pain is the type experienced with tissue damage such as contusion, burn, or injury to a body part.

- *Inflammatory pain:* pain which occurs in response to tissue injury, when inflammation develops and local nociceptors become highly sensitive even to normal stimuli, such as touch. This is another type of "warning" pain, indicating the need for a period of healing, and this pain generally disappears after the injury resolves. In conditions such as rheumatoid arthritis or gout, inflammatory pain persists as long as the inflammation does. (IOM, 2011)

- *Neuropathic Pain*: "pain initiated or caused by a primary lesion or dysfunction of the nervous system." **Neuropathic pain is caused by a malfunction of the peripheral or central nervous system due to an injury or an illness**. (Normal nociception would not be considered dysfunction of the nervous system). The cause may be an underlying disease process (as in diabetes) or injury (e.g., stroke, spinal cord damage), but neuropathic pain may not have an observable cause and can be considered maladaptive "in the sense that the pain neither protects nor supports healing and repair." (Costigan, 2009)

- *Unknown causes:* pain that arises without a defined cause or injury. Examples of such chronic pain conditions are fibromyalgia, irritable bowel syndrome, vulvodynia, chronic headaches, and temporomandibular disorders. Research points to impaired central pain sensitivity and responses in these conditions, but their complex mechanisms have not yet been unraveled. (Kindler, 2011)

Overview

Acute and chronic pain affects large numbers of Americans, with at least 100 million adults in the United States burdened by chronic pain alone. The annual national economic cost associated with chronic pain is estimated to be $560–635 billion. Pain is a uniquely individual and subjective experience that depends on a variety of biological, psychological, and social factors, and different population groups experience pain differentially. (IOM, 2011)

Chronic pain has a significant impact on the individual and on society as a whole, and it is the primary reason for delayed recovery and costs (medical and indemnity) in the workers' compensation system. Most chronic pain problems start with an acute nociceptive pain episode. As a result, effective early care is paramount in preventing chronic pain. Not surprisingly, pain has become the subject of intensive scientific research, and researchers are generating a

growing evidence base regarding the diagnosis, treatment, and management of painful conditions.

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 (pursuit of a pathoanatomical diagnosis with the view of targeting and treating a specific "pain generator") 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. A strictly biomedical approach to pain is simply too reductionist; rather, what is called for is an approach that recognizes the complexity of the pain experience. Similar to what has been learned about other chronic diseases, chronic pain ultimately affects (and is affected by) many intrinsic and extrinsic aspects of a person's life.

In general, the early theories of how pain works failed to address some key issues. (IOM, 2011)

- The relationship between injury and pain varies (that is, a minor injury may produce great pain, and a significant injury may produce minor pain), as does the relationship between the extent of injury and the resulting disability.
- Non-noxious stimuli can sometimes produce pain (allodynia), and minor amounts of noxious stimuli can produce large amounts of pain (hyperalgesia).
- The locations of pain and tissue damage are sometimes different (referred pain).
- Pain can persist long after tissue heals.
- The nature of pain and sometimes its location can change over time.
- Pain is a multidimensional experience, with strong psychosocial influences and impacts.
- Responses to a given therapy vary among individuals.
- Earlier theories have not led to adequate pain treatment.

The biopsychosocial model of pain recognizes that pain is ultimately the result of the patient's pathophysiology and psychological state, cultural background/belief system, and relationship/interactions with the environment (workplace, home, disability system, and health care providers). Therefore, pain has become understood as a complex condition involving numerous areas of the brain. Multiple two-way communication pathways in the central nervous system (from the site of pain to the brain and back again) and emotional, cognitive, and environmental elements work together to form a complete, interconnected pain apparatus. Because it has numerous interacting and contributing causes and multiple effects, chronic pain resembles many other chronic diseases. (Gatchel, 2007; IOM, 2011)

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 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 spinal-cortical pathways to the brain. These signals evoke a response in multiple brain systems, a "distributed network," consistent with the variety of physical, cognitive, affective, and reflexive reactions to pain that people experience.

Since multiple 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 model for, and approach to, the management of pain.

In contrast to nociceptive pain, neuropathic pain is "pain initiated or caused by a primary lesion or dysfunction of the nervous system." (Turk, 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, 2001; Martucci, 2014)

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, temporomandibular disorders, and Complex Regional Pain Syndrome (CRPS)/Reflex Sympathetic Dystrophy (RSD). (Barad, 2014; Mackey, 2004; Ung, 2012; Younger, 2010)

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 neuronal excitability and responsiveness in the dorsal horn increase. In central sensitization, chemical mediators for inflammation can also upregulate the expression of genes that alter synaptic transmission.

Current research indicates that because of neuronal plasticity, 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 for understanding pain. They serve to establish parameters for reasonable outcomes and acceptable guidance for care, which 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 differs from acute pain in 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 involve changes in central pain processing mediated through mechanisms of neural plasticity and may ultimately lead 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 “the distinction between acute and chronic pain is somewhat arbitrary” and “chronicity may be reached from one to six months post injury.” ACOEM states that “chronic pain persists beyond the usual course of healing of an acute disease or beyond a reasonable time for an injury to heal.” (ACOEM, 2014) The definition of chronic pain, “any pain that persists beyond the anticipated time of healing,” is derived from Bonica’s Management of Pain. (Turk, 2001) The MTUS defines chronic pain as pain lasting three (3) or more months from the initial onset of pain. Additional clinical factors that aid in the diagnosis of chronic pain are: (1) when the condition is not improving over time; (2) when there is a lack of improvement 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 (refer to the relevant Clinical Topics section of the MTUS).

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 liability, catastrophizing, job dissatisfaction, perceived injustice, 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 often 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 physical 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) According to this model, 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 the prevailing approach has been 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, 1993)

Pain Models

Biomedical model	**Biopsychosocial model**
Most appropriate for treating 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
Focuses on physical disease mechanisms	Recognizes the importance of illness behavior including cognitive and emotional responses to pain
Takes a reductionistic approach to understanding and treating pain	Takes a multidimensional systems approach to understanding and treating pain
Relies on medical management approaches	Uses self-management approaches in addition to medical management

Researchers have found 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 or protracted, the clinician should consider the possibility of delayed recovery and be prepared to address any confounding psychosocial variables.

Medical vs. Self-Management Model

Understandably, patients want their chronic pain "cured" or eliminated. Unfortunately, no definitive cures currently exist for the majority of persistent pain problems, such as axial spine pain, peripheral neuropathies, and fibromyalgia. As is the case with all chronic medical conditions, chronic pain must be managed, when it cannot be cured. In the medical model, responsibility resides primarily with the physician. However, emphasis is increasingly being placed on encouraging patients to accept some pain and to make self-management efforts that can improve function and quality of life, even if they don't eliminate all pain. An approach that emphasizes participation in daily activities despite pain as well as fostering a willingness to have pain present without responding to it may aid in reducing the "distressing and disabling influences of pain." (Institute of Medicine, 2011) The self-management approach places primary responsibility on the person with chronic pain. 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 to avoid persistent and unrealistic expectations for an elusive cure when none exists. This unrealistic curative view, often unwittingly fostered by healthcare providers, predictably leads to repeated failures, delayed recovery, and unnecessary disability and costs.

Self-efficacy is a psychological construct related to that of control. Believing that one can perform a task or respond effectively to a situation predicts pain tolerance and improvements in physical and psychological functioning. Research suggests that "a primary aim of chronic low back pain rehabilitation should be to bring about changes in catastrophic thinking and self-efficacy," because greater self-efficacy improves pain, functional status, and psychological adjustment. (Keefe, 2004) Researchers posit several explanations for why self-efficacy works to control pain, including the theory that people who expect success are less likely to be stymied when confronting the challenge of pain.

The goals of self-management and self-efficacy reinforce the benefits that accrue when people take a more active role in managing their pain. While self-efficacy as a sole method may not be sufficient to achieve pain control in many situations, treatment should include efforts to help patients actively manage pain.

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 more aggressively managed to avoid ineffective treatment and needless disability. Factors that help identify at-risk patients include: (1) those unresponsive to conservative therapies demonstrated to be effective for specific diagnoses in others; (2) the presence of significant psychosocial factors negatively impacting recovery; (3) loss of employment or prolonged absence from work (which has a high predictive value); (4) previous history of delayed recovery or incomplete rehabilitation; (5) lack of employer support to accommodate patient needs; and (6) a history of childhood abuse (verbal, physical, sexual, etc.) abandonment, or neglect (adverse childhood experience, or ACE).

Subacute Delayed Recovery

Complaints of pain are the most common obstacles 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 (e.g., overtreatment), familial, economic, and psychological consequences (e.g., depression and 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 to resources capable of addressing psychosocial barriers to recovery.

Increasingly, time-limited Cognitive Behavioral Therapy (CBT) is being used successfully to do just that. Literature review meta-analysis has shown the CBT model of intervention to be more effective than wait list controls and alternative active treatment. (Morely,1999) Both the cognitive and behavioral intervention components of CBT have been found effective.

The behavioral component of CBT focuses on physiologic self-management techniques such as reinforcement for participation in functional activities, progressive relaxation, and autogenic/self-hypnosis. These techniques decrease the stress arousal response system associated with chronic pain. CBT techniques may be especially effective for patients with high stress arousal response, guarding behavior and history of ACE.

Patients with Intractable Pain

Studies have shown that the longer a patient remains out of work the less likely he or she is to return. Similarly, the longer a patient suffers from chronic pain the less likely treatment, including functional restoration efforts, will be effective. Nevertheless, if a patient is highly motivated and prepared to make the effort, a multidisciplinary evaluation for admission for treatment in a functional restoration program, (consistent with California Health and Safety Code section 124960) should be considered.

Assessment Approaches

History and Physical Examination

The treating physician has limited sources of objective information. Therefore, it is important for the physician to take a thorough history in clinical assessment and treatment planning for the patient with chronic pain. Whenever possible, this history should include a review of medical records. Clinical recovery may be dependent upon identifying and addressing previously unknown or undocumented medical and/or psychosocial conditions. A thorough physical examination is also important to establish or confirm diagnoses and to observe and better understand pain behaviors. 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 any clinically significant contraindications, the physician should encourage the patient to engage in an active rehabilitation and self-management program. Effective treatment of the chronic pain patient

requires familiarity with patient-specific past diagnoses, treatment outcomes, persistent complaints and psychosocial variables.

Evaluation of Psychosocial Factors

Psychosocial factors have proven better predictors of chronicity than clinical findings. Such variables/factors can and should be assessed; they include a 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/worksite factors.

Childhood trauma may contribute significantly to pain chronicity. A 2010 CDC Study of 26,000 Americans adults revealed that 60% reported childhood familial problems, 15% experienced physical abuse, more than 12% had been sexually abused, and nearly 9% had at least five ACE episodes, (CDC, 2010). Such events (per the ongoing ACE study) correlate with delayed recovery and poor outcomes from injury. Clearly, assessment of psychosocial factors is a critical element of patient evaluation.

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 that can be managed with straightforward interventions and do not require multi-disciplinary treatment. However, for patients with more refractory problems and sufficient motivation, a multidisciplinary, functionally oriented (not pain-oriented) treatment approach with a goal of independent self-management may be a more effective treatment approach. (Flor, 1992; Guzman, 2001)

Functional restoration is an established treatment approach that aims to minimize the residual complaints and disability resulting from acute and chronic medical conditions. Functional restoration may be considered if there is a delay in return to work or a prolonged period of inactivity. Functional restoration is the process by which the individual acquires the skills, knowledge, and behavioral changes necessary to avoid preventable complications and assume or re-assume primary responsibility (“locus of control”) for his or her physical and emotional well-being post injury. The focus is on increasing activities of daily living (ADL), including returning to work. The individual thereby maximizes functional independence and the pursuit of vocational and avocational goals, as measured by functional improvement (see 8 CCR § 9792.20 (e)).

Independent self-management is the long-term goal of all forms of functional restoration. The process and principles of functional restoration can apply to a wide range of conditions, including acute injuries (e.g., sports, occupational), catastrophic injuries (e.g., brain and spinal cord injury), and chronic conditions (e.g., chronic pain and multiple sclerosis).

It should be emphasized that functional restoration is not necessarily a full-time, multi-week treatment program, but rather an approach that emphasizes patient empowerment and personal responsibility.

A coordinated, goal-oriented, functional restoration approach can incorporate pharmacologic treatment, therapeutic interventions, CBT, and physical rehabilitation.

Using medications in the treatment of pain requires a thorough understanding of the mechanism underlying the pain as well as the identification of comorbidities that might predict an adverse outcome (refer to the "MTUS Opioids Treatment Guidelines"). Choice of pharmacotherapy must be based on the type of pain to be treated, though more than one pain mechanism may be 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 responsibility to be well informed about the medication and confident that its use is scientific and evidence based. When effective, medications should provide a degree of analgesia that allows the patients to engage in rehabilitation, improvement of basic activities of daily living, and/or possibly return to work. No drugs have been proven to reverse, cure, or "heal" chronic pain. In addition, periodic review of the ongoing chronic pain treatment plan for the injured worker is essential.

When choosing an invasive procedure to treat a specific chronic pain problem, the provider must make a complex judgment in order to ensure that the desired and expected outcome is worth the risk involved.

Please refer to Part 2 of the Chronic Pain Treatment Guidelines 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. The treatment must be tailored to the individual case. Regardless of who is providing the treatment, be it an individual provider, a multidisciplinary group of providers, integrated interdisciplinary pain program, or a functional restoration 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 to justify continued treatment.

Pain Outcomes and Endpoints

Because pain is a subjective experience, it cannot be readily validated or objectively measured. (AMA, 2001) Therefore, unlike many other chronic diseases, which may have objective measurements that can be used to assess the extent of the problem and treatment outcomes, chronic pain has no objective measurement. Measuring a patient's pain requires correlating objective data with the patient's subjective reporting to arrive at a comprehensive outcome representing the state of pain.

Complicating the measurement of pain is that there is often a wide variability in how much pain a given stimulus or injury will cause. This variability is influenced by genetics, mood, beliefs, sex, ethnicity, and other factors such as early-life experiences with pain. (Kim, 2004)

Chronic pain is often associated with an overall reduction in the patient's quality of life which may lead to depression, anxiety, impaired social and physical function, and sleep disturbance. Moreover, there appears to be relative independence between pain and these co-existing stressors. Therefore, to capture the pain experience, it is necessary to also define and characterize these related domains. (Malhotra, 2012) In addition, it is essential to understand the extent to which pain impedes function. (AMA, 2001)

The physician treating patients 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 the patient is no longer entitled to future medical care. The physician should periodically review the patient's course of treatment 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 the patient's progress toward treatment objectives. If it is unsatisfactory, the physician should assess how appropriate it is to continue the current treatment plan and whether to consider other therapeutic modalities. If the patient taking controlled substances to treat chronic pain experiences decreased pain and can demonstrate increased level of function or improved quality of life, then the treatment has had a satisfactory outcome.

Additionally, fluctuations are likely to occur in the natural history of patients with chronic pain. If exacerbations and "breakthrough" pain occur during the chronic clinical course, adjustments to the treatment will be necessary.

Conclusion

Chronic pain affects approximately 100 million adults in the U.S., with a national economic cost exceeding half a trillion dollars per year. Pain is a uniquely individual and subjective experience. Further, while pain can be a symptom of another condition, when it becomes persistent, it can become a disease in its own right, one that is associated with structural and functional changes of the peripheral and central nervous system. These changes can lead to the generation and maintenance of chronic pain conditions, with associated disability. While biologic mechanisms play a role in the perception of pain, it is important to recognize that psychological and environmental factors play an important role as well. 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 each case.

Therapy for chronic pain ranges from single modality approaches for the straightforward case to comprehensive interdisciplinary functional restoration care for the more challenging case. Therapeutic components such as pharmacologic, interventional, psychological, and physical approaches have been found to be most effective when performed in an integrated manner. All therapies should aim to restore function rather than merely eliminate pain, and demonstrated functional improvement is essential in assessing treatment efficacy. Typically, with increased function comes a perceived reduction in pain and increased perception of its control. These changes ultimately lead to an improvement in the patient's quality of life.

References for Introduction

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Introduction to PART 2

All of the following (listed alphabetically) treatment recommendations are adapted from ODG. For those individual treatment guideline topics where the frequency, duration and intensity of the treatment are not addressed, the following principles apply as set forth in PART 1: Introduction of these guidelines. Duration of the treatment shall be consistent with the definition of chronic pain as set forth in Section 9792.20(b) and page 2 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 10. With regard to the frequency and intensity requirements, the treating physician is required, as stated in the Introduction of these guidelines at page 10, 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 10 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 11.

PART 2:Official Disability Guidelines (ODG) Treatment in Workers' Compensation —Pain (Chronic)

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Acetaminophen (APAP)	Recommended for treatment of acute pain, 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. *Acute pain:* Recommended as an initial choice for treatment of acute pain. See Medications for acute pain (analgesics). *Osteoarthritis:* 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

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	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, 2006) See NSAIDs; NSAIDs, GI symptoms & cardiovascular risk; & NSAIDs, hypertension and renal function. Also see specific body-part chapters in the MTUS. *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 ≥ 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× 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) Acetaminophen may have more risks than originally thought, particularly when it is taken at the higher end of standard therapeutic doses. (Wise, 2015) *Dose:* Acetaminophen has been shown definitively to work synergistically with opioids, enhancing pain relief in a way that is opioid-sparing. (FDA, 2008) Despite acetaminophen's synergistic effect with opioids, fixed combination products are problematic because it is not possible to titrate the opioid dose relative to the acetaminophen dose when the fixed combination is used. Furthermore, in order for acetaminophen to produce an effective analgesic effect, it needs to be used on a regular basis. Consequently, it is best to administer acetaminophen as a single drug and on a routine basis and then, if necessary, to add an opioid as a single entity that may be titrated to effect. (Ray, 2013) *Dose:* The recommended dose for mild to moderate pain is 650 to 1000 mg orally every 6 hours with a FDA-approved maximum of 4 g/day. In calculating the maximum daily dose, it is necessary to combine all sources of acetaminophen in, including many OTC preparations as well as many common opioid combinations that include acetaminophen. An FDA advisory committee has recommended new restrictions on

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	acetaminophen, voting that the single adult acetaminophen dose should be no more than 650 mg with a maximum total dose for 24 hours, decreased to no more than 3,250 mg. (FDA, 2009) The FDA asked drug manufacturers to limit the strength of acetaminophen in prescription drug products, predominantly combinations of acetaminophen and opioids, to 325 mg per pill, to reduce the risk of severe liver injury and allergic reactions. A Boxed Warning has been added to the label of all prescription drug products that contain acetaminophen. (FDA, 2011) To help encourage appropriate acetaminophen use, the newly implemented dosing instructions of Extra Strength Tylenol® (acetaminophen) have lowered the maximum daily dose from 8 pills per day (4,000 mg) to 6 pills per day (3,000 mg). The dosing interval has changed from 2 pills every 4–6 hours to 2 pills every 6 hours. (McNeil, 2014) Acetaminophen is best administered independently and on a routine basis with, if necessary, an opioid added as a single entity that may be titrated to effect.
Actiq® (oral transmucosal fentanyl lollipop)	Not recommended for chronic non-cancer 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 contraindicated in acute pain; is not for use in chronic pain; and has a Black Box warning for abuse potential. See also Fentanyl.
Acupuncture	See the MTUS Acupuncture Treatment Guidelines for recommendations.
A-delta fiber electrodiagnostic testing	Not recommended. See Quantitative sensory threshold testing (QST) testing.
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.
Alprazolam (Xanax®)	Not recommended for long-term use. See Benzodiazepines. Alprazolam, also known under the trade name Xanax and available generically, is a short-acting drug of the benzodiazepine class used to treat moderate to severe anxiety disorders, panic attacks, and as an adjunctive treatment for anxiety associated with major depression.
Ambien® (zolpidem tartrate)	Ambien® is a brand name for zolpidem tartrate produced by Sanofi-Aventis. See Zolpidem (Ambien®).
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.
Antianxiety drugs	See Anxiety medications in chronic pain.
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)

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	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) (Gijsman, 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 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:* Tricyclic antidepressants are recommended as a first-line option, especially if pain is accompanied by insomnia, anxiety, or depression. (Saarto-Cochrane, 2007) (ICSI, 2007). Other recent reviews recommend 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. Good results were found with duloxetine in treating fibromyalgia (Arnold, 2007). Several 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) Duloxetine is approved by the FDA for treatment of fibromyalgia. (FDA 2010) Another review indicated that there is strong evidence that amitriptyline is effective for fibromyalgia

<table>
<tr><th colspan="2">Procedure Summary — Pain</th></tr>
<tr><th>Procedure/Topic</th><th>Summary of medical evidence</th></tr>
<tr><td></td><td>and suggested that more information is needed regarding the role of SNRIs and SSRIs. (Goldenberg, 2007) Compared with placebo, the SNRIs duloxetine (Cymbalta) and milnacipran (Savella) are slightly more likely to reduce pain in patients with fibromyalgia, according to a new Cochrane meta-analysis, but they are not superior in terms of reducing fatigue and sleep problems or in improving quality of life, and they appear to cause more adverse effects. (Häuser, 2013)
Refer to MTUS Low Back Complaints.
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)
Antidepressant discontinuation: Nearly all classes of antidepressants have been linked to discontinuation reactions that are distinct from recurrence or relapse of underlying psychiatric pathology. It does appear that discontinuation reactions can occur regardless of the particular indication for use. The most common research involves discontinuation of serotonin-reuptake inhibitors (Serotonin-discontinuation syndrome).
Symptoms: Symptoms of discontinuation vary between classes of antidepressants, and between different drugs in the classes. These may include changes in mental/psychological status (confusion, restlessness, agitation, anxiety, worsening of mood, panic attacks, dysphoria, manic symptoms, and decreased level of consciousness), neurological changes (tremor, rigidity, clonus, myoclonus, hyperreflexia, ataxia, and rigidity), autonomic changes (diaphoresis, shivering, mydriasis, nausea and diarrhea), and changes in vital signs (tachycardia, hypertension, hyperthermia, and tachypnea). Commonly patients describe both psychological and somatic symptoms (the latter described as flu-like, with or without gastrointestinal physical symptoms). Symptoms are thought to occur in at least 20% to 25% of patients upon discontinuing of serotonin-reuptake inhibitors (with reports of at least 50% with drugs with shorter half-lives such as paroxetine or venlafaxine). Symptoms tend to emerge within 2 to 5 days with a usual duration of 1 to 2 weeks. The primary risk factors for this reaction include use of antidepressants with shorter half-lives, longer duration of treatment, and abrupt discontinuation.
Differentiation from depression relapse or recurrence: Differentiating factors include looking for symptoms that are more likely to occur with discontinuation reaction (dizziness, electric shock-like sensations, “rushing” sensations, headache and nausea) as well as observing for rapid reversal of symptoms (complete resolution within 1 to 2 weeks of the taper/discontinuation is less likely to be due to depression). Later onset of symptoms (after at least two to three weeks of discontinuation/tapering) or prolonged symptoms (3 weeks or greater) are more commonly associated with a relapse of psychiatric pathology or another intercurrent disease.
SPECIFIC ANTIDEPRESSANTS:
Tricyclic antidepressants are recommended over selective serotonin</td></tr>
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	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, cisplatinum 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) The muscle relaxant cyclobenzaprine is closely related to the tricyclic antidepressants so caution is advised when using cyclobenzaprine. (FDA, 2011) *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)

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	Selective serotonin and norepinephrine reuptake inhibitors (SNRIs): *Duloxetine (Cymbalta®)*: FDA-approved for anxiety, depression, diabetic neuropathy, fibromyalgia and chronic musculoskeletal pain. (FDA, 2010) 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%). 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: (≥ 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

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	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. *Side Effects: Bleeding:* An association has been found between the use of SSRI antidepressants and gastrointestinal bleeding. This risk is increased with the concomitant use of ASA or NSAIDs. It is suggested that the increased risk for GI bleeding be discussed with patients that have other risks for GI bleeding. An association with increased intraoperative blood loss has also been found with SSRI use. (Movig, 2003) A treatment option for those at risk for bleeding includes switching to an antidepressant with a lower degree of inhibition of serotonin reuptake (Intermediate reuptake: venlafaxine, amitriptyline, imipramine, citalopram; Low reuptake: desipramine, doxepin, trazodone, bupropion, mirtazapine). SSRIs with the highest degree of inhibition of serotonin reuptake include paroxetine, sertraline, and fluoxetine. (Looper, 2007)
Antiemetics (for opioid nausea)	Not recommended for nausea and vomiting secondary to chronic opioid use. Recommended for acute use as noted below per FDA-approved indications. Nausea and vomiting is common with use of opioids. These side effects tend to diminish over days to weeks of continued exposure. Studies of opioid adverse effects including nausea and vomiting are limited to short-term duration (less than four weeks) and have limited application to long-term use. If nausea and vomiting remains prolonged, other etiologies of these symptoms should be evaluated for. The differential diagnosis includes gastroparesis (primarily due to diabetes). Current research for treatment of nausea and vomiting as related to opioid use primarily addresses the use of antiemetics in patients with cancer pain or those utilizing opioids for acute/postoperative therapy. Recommendations based on these studies cannot be extrapolated to chronic non-malignant pain patients. There is no high-quality literature to support any one treatment for opioid-induced nausea in chronic non-malignant pain patients. (Moore 2005) *Promethazine (Phenergan®):* This drug is a phenothiazine. It is recommended as a sedative and antiemetic in pre-operative and post-operative situations. Multiple central nervous system effects are noted with use including somnolence, confusion and sedation. Tardive dsykensia is also associated with use. This is characterized by involuntary movements of the tongue, mouth, jaw, and/or face. Choreoathetoid movements of the extremities can also occur. Development appears to be associated with prolonged treatment and in some cases can be irreversible. Anticholinergic effects can occur (dry mouth, dry eyes, urinary retention and ileus). *Ondansetron (Zofran®)*: This drug is a serotonin 5-HT3 receptor antagonist. It is FDA-approved for nausea and vomiting secondary to chemotherapy and radiation treatment. It is also FDA-approved for postoperative use. Acute use is FDA-approved for gastroenteritis. See also Nabilone (Cesamet®), for chemotherapy-induced nausea, but not

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	pain.
Anti-epilepsy drugs (AEDs) for pain	*Anti-epilepsy drugs (AEDs) are also referred to as anti-convulsants.* Recommended for some neuropathic pain (pain due to nerve damage), but not for acute nociceptive pain (including somatic pain). (Gilron, 2006) (Wolfe, 2004) (Washington, 2005) (ICSI, 2005) (Wiffen-*Cochrane*, 2005) (Attal, 2006) (Wiffen-*Cochrane*, 2007) (Gilron, 2007) (ICSI, 2007) (Finnerup, 2007) (Wiffen-Cochrane, 2013) 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®); Lamotrigine (Lamictal®); Carbamazepine (Tegretol®); Oxcarbazepine (Trileptal®); Phenytoin (Dilantin®); Topiramate (Topamax®); Levetiracetam (Keppra®); Zonisamide (Zonegran®); & Tiagabine (Gabitril®) *Outcomes:* 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) Manufacturers of antiepileptic drugs will need to add a warning to their labeling indicating that use of the drugs increases risk for suicidal thoughts and behaviors, according to an FDA Alert issued December 16. (FDA MedWatch, 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)

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	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) *Acute pain:* Not indicated due to lack of evidence. *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 acute musculoskeletal pain, 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) (Wiffen-*Cochrane,* 2013) 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:*

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	Acute pain: There is limited evidence to show that this medication is effective for acute pain, and 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) *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 trails of the two drugs. ***Pregabalin (Lyrica®, no generic available)*** has been documented to be

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	effective in treatment of diabetic neuropathy and postherpetic neuralgia, has FDA approval for both indications, and is considered first-line treatment for both. (Wiffen-*Cochrane*, 2013) 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 different doses and frequencies of pregabalin for painful DPN concluded that pregabalin at increasing daily doses 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) Significant negative cognitive side effects were documented in healthy volunteers at 600 mg per day in one study. (Salinsky, 2010) 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 limited 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

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	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 effect treatments including other AEDs and antidepressants. (Wiffen-*Cochrane*, 2007) *Side-Effect Profile*: Lamotrogine 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 Tigaran, 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) ***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 hematolgic disorders, including agranulycytosis 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

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	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. (ICSI, 2007) Evidence for treating other neuropathies is inconclusive. It is not currently recommended for diabetic peripheral neuropathy or post-herpetic neuralgia. (Dworkin, 2010) *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®, 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) ***Levetiracetam (Keppra®, generic available), Zonisamide (Zonegran®, generic available), and Tiagabine (Gabitril®, no generic),*** 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). Refer to the MTUS Low Back Complaints. 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) See also Nonprescription Medications. COX-2 inhibitors (e.g., Celebrex) may be considered if the

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	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, 2004) For precautions in specific patient populations, see NSAIDs, GI symptoms & cardiovascular risk.
Antispasmodics	See Muscle relaxants.
Antispasticity drugs	See Muscle relaxants.
Anxiety medications in chronic pain	Recommend diagnosing and controlling anxiety as an important part of chronic pain treatment, including treatment with anxiety medications based on specific DSM-IV diagnosis as described below. Benzodiazepines are not recommended for longer than two weeks unless the patient is being seen by a psychiatrist. *Definition of anxiety disorders:* Anxiety disorders for this entry include (1) generalized anxiety disorder (GAD); (2) panic disorder (PD); (3) post-traumatic stress disorder (PTSD); (4) social anxiety disorder (SAD); & (5) obsessive-compulsive disorder (OCD). Descriptions of each are included below. Anxiety affects millions of Americans and leads to a decreased quality of life and productivity. In any given year approximately 40 million American adults ages 18 and older have an anxiety disorder (approximately 18.1 percent). Approximately 62% of anxiety disorders are associated with other mental health disorders, in particular depression. Substance abuse is also a frequent co-morbid condition. *Anxiety and chronic pain:* Anxiety is commonly found in patients with chronic pain, with the most common disorders being specific phobia (12.5% to 15.7%), SAD (8.3% to 11.8%) and PTSD (7.3% to 10.7%). These rates are higher than those found in the general US population. There is some evidence to suggest that anxiety disorders precede the onset of pain. Research is still needed to determine the temporal sequence. (Roy-Byrne, 2008) (Baldwin, 2005) (Bandelow, 2002) (Hoffman, 2008) *Overview of pharmacotherapy:* The anxiety disorders with the greatest evidence for the efficacy of pharmacotherapy are GAD, PD, and SAD, and OCD. There is more limited evidence for pharmacotherapy for PTSD. Many antidepressants, in particular the Selective Serotonin Reuptake Inhibitors (SSRIs) are considered first-line agents in the treatment of most forms of anxiety. They have a more favorable side-effect profile than monamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs). They also have the advantage of treating comorbid depression. Selective Norepinephrine Reuptake Inhibitors (SNRIs), in particular Effexor® (venlafaxine) have also been proven to be effective in the treatment of many anxiety disorders. Benzodiazepines are often used to treat anxiety disorders; however, many guidelines discourage the long-term use of benzodiazepines due to sedation effects and potential for abuse and psychological dependence. Long-term use is often associated with withdrawal symptoms. Some other drug classes used to treat anxiety are antihistamines (e.g. hydroxyzine), 5HT1 agonist (e.g. buspirone), and some anti-epilepsy drugs. *(Specific Treatment: FDA-*

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<tr><td></td><td>approved indications are listed next to each specific drug. A note is made if a medication is used off-label.) (Hoffman, 2008)
(1) GENERALIZED ANXIETY DISORDER (GAD): GAD is characterized by anxiety/tension, excessive worry, restlessness, fatigability, poor concentration, irritability, muscle tension and poor sleep. Treatment for GAD is patient specific and the following serves only as a guide in providing pharmacotherapy. Some patients may require adjunctive psychotherapy, such as cognitive behavioral therapy (CBT) or may prefer psychotherapy, instead of pharmacotherapy. (Zwanzger, 2008) SSRIs or SNRIs are typically first-line agents for GAD. TCAs such as imipramine have been shown to be somewhat effective, but are not recommended as first-line agents due to side effects in particular. Outcomes are measured with tests such as the Hamilton Rating Scale for Anxiety (HAM-A), the Clinical Global Impression Improvement (CGI-I) scale and Clinical Global Impression Severity (CGI-S) scale. (Hoffman, 2008) (Kapczinski-Cochrane, 2003) (Schmitt, 2005)
(a) SSRIs: Escitalopram (Lexapro®, no generic available): also approved for major depressive disorder. Dosing information: 10-20 mg once daily. Paroxetine (Paxil®, generic available): Also recommended for PD, SAD, OCD, and PTSD as well as major depressive disorder. Dosing information: 20-50 mg daily. (Package insert, GlaxoSmithKline) Setraline (Zoloft®, generic available): Studies have shown effectiveness but not FDA-approved for this indication. Dosing information: 50-150 mg daily.
(b) SNRIs: Duloxetine (Cymbalta®, no generic available): also approved for major depressive disorder. Dosing information: 30-120 mg daily. Venlafaxine extended release (Effexor XR®, generic available): also recommended for PD and SAD as well as major depressive disorder. Dosing information: 75-225 mg daily. It may be recommended for some patients to start at 37.5 mg for the first 4 to 7 days. (Package insert)
(c) 5-HT1A Agonist: Buspirone (Buspar®, generic available): also approved for short-term relief of anxiety symptoms. Efficacy is decreased in patients with recent prior benzodiazepine use. (Chessick, 2006) Dosing information: 5-15 mg three times daily. (Package insert)
(d) Benzodiazepines: Effective for acute treatment. Long-term use is problematic as few patients achieve and sustain remission with monotherapy. These agents are used primarily as an adjunct for stabilization during initiation of an SSRI or SNRI. The disadvantage of use is the risk of abuse and physiological dependence with long-term use. These drugs also have no anti-depressant effect. Diazepam (Valium®, generic available): Dosing information: 5-15 mg daily. Clonzaepam (Klonopin®, generic available): Dosing information: 1-2 mg up to TID.
(e) TCAs (Tricyclic antidepressants): This class of medications is an effective treatment for GAD but few studies have investigated their use for DSM-IV defined GAD. Their use is limited by poorer tolerability.
(f) Other medications that may be useful: Hydroxyzine (Atarax®, generic available): Dosing information: 50 mg/day. Pregabalin (Lyrica®,</td></tr>
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<tr><td></td><td>generic available): Non-FDA approved indication. Dosing information: 50-200mg three times daily (with a general range of 200-450 mg a day) Atypical antipsychotics: Olanzapine (Zyprexa®) and Risperidone (generic available): used as an adjunct agent.
(2) <u>PANIC DISORDER (PD) with and without agoraphobia</u>: Panic disorder (PD) is described by the DSM-IV-TR to include periods of intense fear that peak within 10 minutes. Symptoms include palpitations, sweating, shortness of breath and lightheadedness. Patients often have persistent worry about having further attacks. PD can occur with or without agoraphobia (anxiety about and avoidance of being in situations where escape may be difficult). Outcomes are measured in terms of frequency and change in the total number of attacks. Testing includes the Panic Disorder Severity Scale (PDSS). (Hoffman, 2008) (Mitte, 2005) (Otto, 2001) (Furukawa, 2007)
(a) <u>Maintenance treatment</u>: SSRIs are first-line medications based on safety and tolerability. If the patient does not respond, another SSRI should be attempted. If this fails, another class of medications should be attempted (SNRI, TCA or benzodiazepine). Fluoxetine (Prozac®, generic available): Also approved for major depressive disorder, OCD and premenstrual dysphoric disorder. Dosing information: 20-60 mg daily. Paroxetine (Paxil®, generic available): Also recommended for GAD, SAD, OCD, and PTSD as well as major depressive disorder. Dosing information: dosing is typically 10-60 mg daily. Paroxetine CR (Paxil® CR): Also approved for SAD, major depressive disorder, and premenstrual dysphoric disorder. Sertraline (Zoloft ®, generic available): Also approved for PTSD, SAD, OCD, major depressive disorder and premenstrual dysphoric disorder. Dosing information: 50-200 mg once daily. Citalopram (Celexa®, generic available): Non-FDA approved indication. Dosing information: 20-60 mg once daily. Fluvoxamine (Luvox®, generic available): Non-FDA approved indication. Dosing information: Initially 50mg at bedtime, doses should be titrated upward to daily doses of 100-300 mg daily. Daily doses greater than 100mg should be divided, with the larger dose given at bedtime. Escitalopram (Lexapro®): Non-FDA approved indication. Dosing information: 10-20 mg once daily. <u>SNRI</u>: Venlafaxine (Effexor XR®, generic available): also approved for GAD, SAD and major depressive disorder. Dosing information: 37.5-225 mg daily.
(b) <u>Secondary treatment options</u>, when other medications have failed or been intolerable to patients: <u>Tricyclic Antidepressants (TCAs)</u>: Clomipramine (Anafranil®, generic available): Dosing information: 75-250 mg daily. (Bandelow, 2002) Imipramine (Tofranil®, generic available): Dosing information: 75-250 mg daily. (Bandelow, 2002) <u>MAOI</u>: Phenelzine (Nardil®, no generic available): Dosing information: 45-90 mg daily in divided doses, three times daily. <u>Other anti-depressants</u>: Mirtazapine (Remeron®, generic available): Dosing information: 45 mg daily.
(c) <u>Acute treatment</u>: Benzodiazepines may be recommended with initial</td></tr>
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<tr><td></td><td>treatment as an adjunct agent to SSRIs as the latter class of drugs is titrated. Benzodiazepines (short acting): Alprazolam (Xanax®, generic available): Dosing information: 0.25-1 mg TID or QID. Clonazepam (Klonopin®, generic available): Dosing information: 1-4 mg daily in two divided doses. The dose should be tapered downward during discontinuation by 0.125mg twice daily every 3 days. Doses of 1 mg are just as effective as higher doses, with less adverse effects. However, some patients may benefit from higher doses. (Roche Laboratories, 2001)
(3) POST-TRAUMATIC STRESS DISORDER (PTSD)
Characterized in DSM-IV by three symptom clusters which persist for more than one month, and cause clinically significant distress: re-experiencing the event; emotional numbing/avoidance of stimuli associated with trauma; and hyperarousal. DSM-V adds another cluster, negative alterations in cognitions and mood associated with the traumatic event.
Most clinical guidelines recommend pharmacotherapy as a first-line treatment for PTSD. Long-term trials show that while 30% of patients remit within 12 weeks, a substantial percentage does not achieve remission within 6 months (Friedman, 2013
(a) SSRIs: considered first-line agents in the treatment of PTSD. Paroxetine (Paxil®, generic available): Also recommended for GAD, SAD, OCD, and PD as well as major depressive disorder. Dosing information: 20-50mg daily (Bandelow, 2002) (PPI GlaxoSmithKline, 2004) Sertraline (Zoloft ®, generic available): Also approved for PD, SAD, OCD, major depressive disorder and premenstrual dysphoric disorder. Dosing information: 50-200mg daily. Fluoxetine (Prozac®, generic available): Dosing information: 20-40mg daily. (Bandelow, 2002) (Clinical Pharmacology, 2008)
(b) TCAs: Amitriptyline (Elavil®, generic available): Dosing information: 75-200mg daily.
(c) Other antidepressants Venlafaxine (Effexor-XR) is effective for symptoms of PTSD, and is associated with improved resilience (Davidson, 2006). Mirtazapine, an antidepressant with both serotonergic and adrenergic activity has proven efficacy for PTSD, and is recommended as a second-line agent (Friedman, 2013). Trazodone may be used in conjunction with SSRIs to counter medication induced insomnia.
(d) Alpha-1 Adrenergic Agents: Prazosin, is effective for hyperarousal symptoms, including nightmares of PTSD. (Raskind, 2003, 2007)
(e) Topiramate has a broad spectrum effect on PTSD symptoms, comparable to other psychopharmacological agents. (Akuchekian, 2004), (Tucker, 2007), (Yeh, 2011)

Antipsychotics like Risperidone may be beneficial as an adjunct treatment.

Benzodiazepines are not recommended for PTSD, unless they are needed for comorbid disorders.

(4) SOCIAL ANXIETY DISORDER (SAD):</td></tr>
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	The DSM-IV-TR describes generalized SAD as a persistent fear of social situations, with exposure leading to anxiety and avoidance. *Outcomes:* Most studies have used the Liebowitz Social Anxiety Scale (LSAS). (Hoffman, 2008) (Schneier, 2006) (Hedges, 2007) (Ipser, 2008) ***(a) SSRIs:*** generally recommended as first-line agents for treating SAD, due to effectiveness and favorable side effect profile. The initial dose is generally half of the usual dose. Titration can occur over 1 week to 4 weeks. A trial of a SSRI is recommended for at least 12 weeks as some patients take over 8 weeks for a response. Maintenance therapy is recommended for those patients who take over 8 weeks for response to prevent relapse. Medications are indicated for at least 6 to 12 months with follow-up for relapse. (Schneier, 2006) ***Paroxetine (Paxil®, generic available):*** Also recommended for GAD, PD, OCD, and PTSD as well as major depressive disorder. *Dosing information:* 20-60mg daily. (Bandelow 2002) ***Paroxetine controlled release (Paxil CR®, generic available):*** Also approved for PD, major depressive disorder, and premenstrual dysphoric disorder. *Dosing information:* Initially 12.5 mg daily, may increase up to 37.5mg daily. (PPI GlaxoSmithKline) ***Sertraline (Zoloft®, generic available:*** Also approved for OCD, major depressive disorder and premenstrual dysphoric disorder. *Dosing information:* 50-150 mg daily (max 200 mg daily). ***Escitalopram (Lexapro®, no generic available):*** Non-FDA approved indication. *Dosing information:* 10-20 mg once daily. ***Fluvoxamine (Luvox®, generic available):*** Non-FDA approved indication. *Dosing information:* Initially 50 mg at bedtime, doses should be titrated upward to daily doses of 100-300 mg daily. Daily doses greater than 100 mg should be divided, with the larger dose given at bedtime. ***(b) SNRI:*** Considered a first-line medication for generalized SAD. ***Venlafaxine (Effexor XR®, generic available):*** also approved for GAD, PD and major depressive disorder. *Dosing information:* 37.5-225mg daily. Generally started at half of the usual dose and increased over the first week of treatment. Doses can then be increased over a 4-week period. ***(c) Other agents used as secondary or alternative treatment to SSRIs:*** (Schneier, 2006) Benzodiazepines: ***Clonazepam (Klonopin®, generic available):*** *Dosing information:* See Generalized Anxiety Disorder. Anticonvulsants: ***Gabapentin (Neurontin®, generic available):*** non-FDA approved indication. *Dosing information:* 900-3600 mg per day in divided doses. ***Pregabalin (Lyrica®):*** Non-FDA approved indication. *Dosing information:* 300-600 mg. **(5) OBSESSIVE COMPULSIVE DISORDER (OCD):** Characterized by recurrent obsessional ruminations, images or impulses, and/or recurrent physical or mental rituals. These ruminations interfere with social and occupational function. OCD is thought to respond selectively to drugs that inhibit the synaptic reuptake of serotonin. An adequate trial should consist of 10-12 weeks with at least 4-6 weeks at the maximum tolerated dose. Cognitive-behavioral therapy may need to be considered. (Soomro, 2008) (Baldwin, 2005) ***(a) SSRIs: Fluoxetine (Prozac®, generic available):*** *Dosing*

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	information: 20-80 mg daily, doses greater than 40 mg daily should be divided. ***Fluvoxamine (Luvox®, generic available):*** *Dosing information:* doses should be titrated to a range of 100-300 mg, with doses greater than 100 mg daily in divided doses. ***Paroxetine (Paxil®, generic available):*** *Dosing information:* Initially 20mg (optimal dose is 40mg/day); max dose is 60mg daily. ***Sertraline (Zoloft®, generic available):*** *Dosing information:* 50-200 mg daily. ***(b) TCAs: Clomipramine (Tofranil®, generic available):*** *Dosing information:* Initially 25 mg daily, dose should be titrated upward to doses from 75-250 mg daily. Dose may be given at bedtime to reduce the incidence of daytime sedation. Note: During the initial titration of clomipramine, the dose may be given in divided daily doses in order to minimize GI effects. (PPI Mallinkrodt Inc.) ***(c) Benzodiazepines for severe cases, treatment resistant cases or adjunctive therapy: Clonazepam (Klonopin®, generic available).*** ***(d) Other agents used for treatment resistant patients (Adjunct therapy):*** If there is no response to one of the above drugs, the suggestion is to try another first-line alternative. Then adjunct therapy is suggested. This includes the combination of a SSRI and clomipramine, or the use of one of the above with a benzodiazepine, buspirone, antipsychotic, or mood stabilizer. If there is no response a MAOI inhibitor may be required. (Dell'Osso, 2007)
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 therapy. 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)
Armodafinil (Nuvigil)	Not recommended solely to counteract sedation effects of narcotics. Armodafinil is used to treat excessive sleepiness caused by narcolepsy or shift work sleep disorder. It is very similar to Modafinil. Studies have not demonstrated any difference in efficacy and safety between armodafinil and modafinil. (Tembe, 2011) For more information see also Modafinil (Provigil®), Recently Cephalon produced a campaign advertising Nuvigil's ability to help shift workers stay alert on the job without impeding their ability to sleep during the day. The FDA is conducting an investigation into the possibility that this advertising or promotional information may have violated current regulations. (SEC, 2011).
Arthrotec® (diclofenac/	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function;

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misoprostol)	& NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Arthrotec® (diclofenac/ misoprostol) listing for more information and references. See also Diclofenac, where it is not recommended as first line due to increased risk profile. The package insert for Arthrotec includes a boxed warning that also relates to potential toxicities of misoprostol. In the treatment of NSAIDs induced ulcers, omeprazole has proved to be at least as effective as misoprostol, but significantly better tolerated, and therefore misoprostol should not be considered a first choice treatment. (FDA, 2011)
Aspirin	Recommended. See Nonprescription medications; & Medications for acute pain (analgesics). Usual Adult Dose for Pain: 325 to 650 mg every 4 hours as needed, up to 3 grams per day in divided doses (spondyloarthropathies may require up to 4 grams per day in divided doses). (FDA, 2012)
Auricular electroacupuncture	Not recommended. The evidence is insufficient to evaluate the effect of auricular electroacupuncture on acute and chronic pain. In the only published RCT, use of the P-Stim device was not associated with improved pain management. Auricular electrostimulation or ear-acupuncture is a type of ambulatory electrical stimulation of acupuncture points on the ear. Devices, including the P-Stim™ and E-pulse, have been developed to provide continuous or intermittent stimulation over a period of several days. This type of electrostimulation is being evaluated for a variety of conditions, including pain, depression, and anxiety. Both the P-Stim (NeuroScience Therapy Corp) and the E-pulse (AMM Marketing LLC) devices have received marketing clearance through the FDA abbreviated 510(k) process for use in treating acute or chronic pain by a qualified practitioner of acupuncture. (Holzer, 2011) (Zhang, 2014) (Sator-Katzenschlager, 2007) see also Acupuncture.
Autonomic nervous system function testing	Not generally recommended as a diagnostic test for CRPS. See CRPS, diagnostic tests.
Autonomic test battery	Not generally recommended as a diagnostic test for CRPS. See CRPS, diagnostic tests.
Avinza® (morphine sulfate)	Refer to MTUS Opioids Treatment Guidelines for recommendations on the use of opioids. Avinza capsules are a brand of modified-release morphine sulfate. The capsules contain an immediate-release component that rapidly achieves a morphine concentration and an extended-release component that allows for extended concentration through a 24-hour dosing interval. *Use:* It takes approximately 2-3 days to achieve steady state and this drug is not recommended as an as needed (prn) drug or for acute pain. The manufacturer now specifically states that the 90 mg and 120 mg capsules are only recommended for patients for whom a tolerance to an opioid of comparable potency is established. A maximum dose of this drug has been established at 1600 mg due to the presence of fumaric acid. *Comparison to other opioids (including extended-release and immediate-release morphine):* There is one study that compares the pharmacokinetics of Avinza to MS Contin (the latter at a twice-a-day dose). This study was open-label and non-randomized. Clinical efficacy and

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	safety were comparable for both formulations. (Portenoy, 2002) The original researchers indicated that analgesia was statistically identical to that produced by MS Contin, OxyContin and six doses of oral morphine sulfate administered every 4 hours. (Caldwell, 2004) *Black Box Warning:* The current Black Box Warning for Avinza is that patients must not consume alcohol with this drug (including that included in prescription and non-prescription medications). Consumption of alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. (FDA, 2008) The current FDA Orange Book (accessed March 2013) has determined that actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence.
Axon-II neural scan	Not recommended. See Quantitative sensory threshold (QST) testing.
Baclofen	See CRPS, treatment. 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) Fioricet is commonly used for acute headache, with some data to support it, but there is a risk of medication overuse as well as rebound headache. (Friedman, 1987) The AGS updated Beers criteria for inappropriate medication use includes barbiturates. (AGS, 2012) See also Opioids.
Behavioral interventions/ Cognitive Behavioral Therapy (CBT)	Recommended. Please review Introduction to the MTUS Chronic Pain Guidelines for background on psychosocial variables and their potential role in delayed recovery and chronic pain. Risk Factors for delayed recovery include catastrophic thinking, fear-avoidance, and perceived injustice. 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. Several recent reviews support the assertion of efficacy of cognitive-behavioural therapy (CBT) in the treatment of pain, especially chronic back pain (CBP). (Kröner-Herwig, 2009) The CBT treatment model has three stages: (1) skill education (2) skill acquisition and (3) skill maintenance / generalization. Homework assignments are an essential part of CBT. When possible, CBT should be coordinated with physical therapy. There are no studies that delineate specific quantity and frequency of CBT sessions for chronic pain. Please refer to the ODG Psychotherapy Guidelines (just below) for further recommendations. Please refer to the MTUS Opioids Treatment Guidelines and MTUS Low Back Complaints and Stress-Related Conditions. **ODG Psychotherapy Guidelines:** - Up to 13-20 visits over 7-20 weeks (individual sessions), if progress is being made. (The provider should evaluate symptom improvement during the process,

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	so treatment failures can be identified early and alternative treatment strategies can be pursued if appropriate.) - In cases of severe Major Depression or PTSD, up to 50 sessions if progress is being made.
Benzodiazepines	Not recommended for long-term use because long-term efficacy is unproven and there is a risk of psychological and physical dependence or frank addiction. Most guidelines limit use to 4 weeks. Benzodiazepines are a major cause of overdose, particularly as they act synergistically with other drugs such as opioids (mixed overdoses are often a cause of fatalities). 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 (3-14 day). 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. Tolerance to lethal effects does not occur and a maintenance dose may approach a lethal dose as the therapeutic index increases. The best prevention for substance use disorders due to benzodiazepines is careful prescribing. (Baillargeon, 2003) (Ashton, 2005) (Dickinson, 2009) (Lader, 2009) Adults who use hypnotics, including benzodiazepines such as temazepam, have a greater than 3-fold increased risk for early death, according to results of a large matched cohort survival analysis. The risks associated with hypnotics outweigh any benefits of hypnotics, according to the authors. In 2010, hypnotics may have been associated with 320,000 to 507,000 excess deaths in the U.S. alone. A dose-response effect was evident, with a hazard ratio of 3.60 for up to 18 pills per year, 4.43 for 18-132 pills per year, and 5.32 for over 132 pills per year. (Kripke, 2012) The AGS updated Beers criteria for inappropriate medication use includes benzodiazepines. (AGS, 2012) See also Anxiety medications in chronic pain; & Insomnia treatment. Benzodiazepines that are commonly prescribed include the following: alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, & triazolam. (Clinical Pharmacology, 2010) **Benzodiazepines are Not Recommended as first-line medications by ODG.** **Criteria for use if provider & payor agree to prescribe anyway:** 1) Indications for use should be provided at the time of initial prescription. 2) Authorization after a one-month period should include the specific necessity for ongoing use as well as documentation of efficacy.
Benzodiazepine dependence, maintenance	Recommended for selected patients, due to risks of weaning. Early research indicates that switching from rapid-onset, short-acting benzodiazepines to slow-onset, long-acting formulations is an option. In some cases this will actually allow for ultimate discontinuation of this class of drugs. Clonazepam is the suggested drug to switch to. It has a slow onset of action, half-life of 18-50 hours, high potency and lack of active

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	metabolites. (Liebrenz, 2010) (Maremmani, 2013) See also Weaning, benzodiazepines (specific guidelines).
Bier's block	See Intravenous regional sympathetic blocks (for RSD/CRPS).
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, 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) Functional MRI has been proposed as a method to control brain activation of pain. See Functional imaging of brain responses to pain. **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 therapy 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)

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	- Patients may continue biofeedback exercises at home
Biopsychosocial model of chronic pain	See Introduction to the MTUS Chronic Pain Guidelines for a definition and detailed description. Chronic pain programs (multidisciplinary pain programs or functional restoration programs), are recommended for patients with conditions that put them at risk of delayed recovery where there is access to programs with proven successful outcomes.
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 moblity. The effects may potentially involve avenues other than inhibition of bone resorption. (Manicourt, 2004) However, use has been associated with complications including osteonecrosis of the jaw and possible increased risk of long bone fractures including the femur. (Mehrotra, 2006) 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.
Bone scan (for CRPS)	See CRPS, diagnostic tests.
Boswellia Serrata Resin (Frankincense)	Recommended as an option for knee osteoarthritis, but more studies are needed to validate early results. A statistically significant improvement in arthritis of the knee was shown after 8 weeks of treatment with 333 mg B. serrata extract taken three times a day. The treatment improved function, but radiographically there was no change in the affected joints. (Maroon, 2006) This RCT concluded that 5-Loxin (a proprietary version of Boswellia serrata extract enriched with 30% AKBA) reduces pain and improves physical functioning significantly in patients with osteoarthritis of the knee, and it is safe for human consumption. (Sengupta, 2008)
Botox	See Botulinum toxin.

Botulinum toxin (Botox®; Myobloc®)	Not recommended for most chronic pain conditions. See more details below and refer also to specific MTUS body chapters. *Not recommended for the following: tension-type headache; fibromyositis; chronic neck pain; myofascial pain syndrome (MPS); & trigger point injections.* Studies have found no statistical support for the use of Botulinum toxin A (BTX-A) for those conditions. *Myofascial pain syndrome (MPS):Not recommended:* No myofascial analgesic pain relief as compared to saline. (Qerama, 2006) No success as a specific treatment for myofascial cervical pain as compared to saline. (Ojala, 2006) (Ferrante, 2005) (Wheeler, 1998) No success from injection in myofascial trigger points as compared to dry needling or local anesthetic injections. (Kamanli, 2005) (Graboski, 2005). 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 pain (as compared to saline). (Peloso-*Cochrane*, 2006) One study 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) Other more recent reviews find inconclusive evidence to support the use of botulinum toxin in the treatment of MPS. (Soares *Cochrane*, 2014) Contradictory study results regarding the efficacy of Botulinum toxin A in MPS associated with neck and back pain do not allow this treatment to be recommended or rejected. (Climent, 2013) *Low back pain:* Refer to the MTUS Low Back Complaints. *Cervical dystonia: Recommended:* This is a condition that is not generally related to workers' compensation injuries (also known as spasmodic torticolis), 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, highantigenicity 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. See the MTUS Neck and Upper Back Complaints for cervical dystonia references. *Spinal cord injury: Recommended: urinary incontinence following spinal cord injury.* Botox significantly reduced urinary incontinence and improved urodynamics and quality of life in spinal cord injury and multiple sclerosis patients with neurogenic detrusor overactivity. (Cruz, 2011) Botulinum toxin is well tolerated and provides clinically beneficial improvement for urinary incontinence and neurogenic detrusor overactivity secondary to spinal cord injury or multiple sclerosis. (Herschorn, 2011) There are other potential roles in spinal cord injury with spasticity. (Marciniak, 2008) *Migraine: Recommended for prevention of headache in patients with chronic migraine.* Chronic migraine is defined as having a history of migraine and experiencing a headache on most days of the month. (FDA, 2010) A systematic review of RCTs concluded that Botulinum toxin A compared with placebo was associated with a small to modest benefit for chronic daily headaches and chronic migraines but was not associated with fewer episodic migraine or chronic tension-type headaches per

	month. (Jackson, 2012) The FDA approved Botox injection (onabotulinumtoxinA) to prevent headaches in adult patients with chronic migraine. It is recommended as a second line therapy (since other acute therapies should have been attempted).
Bretylium	See Bier's block.
Buprenorphine	See Buprenorphine for treatment of chronic pain; Buprenorphine for treatment of opioid dependence.
Buprenorphine for chronic pain	Recommended as an option for treatment of chronic pain (consensus based) in selected patients (not first-line for all patients). *Suggested populations:* (1) Patients with a hyperalgesic component to pain; (2) Patients with centrally mediated pain; (3) Patients with neuropathic pain; (4) Patients at high-risk of non-adherence with standard opioid maintenance; (5) For analgesia in patients who have previously been detoxified from other high-dose opioids. Use for pain with formulations other than Butrans is off-label. Due to complexity of induction and treatment the drug should be reserved for use by clinicians with experience. *Drug description:* Buprenorphine is a schedule-III controlled substance. Its mechanism of action is complex, involving four different opioid receptors at central and peripheral sites. It is primarily classified as a partial mu-agonist and kappa antagonist. It blocks effects of subsequently administered opioid agonists. There is the potential for buprenorphine to precipitate withdrawal in opioid-experienced patients. ***Available formulations**:* *Buprenorphine hydrochloride injection (Buprenex®; generics available).* *Buprenorphine hydrochloride sublingual tablets (Subutex® [innovator brand is off market]; generics available):* 2 mg and 8 mg. *Buprenorphine hydrochloride and naloxone hydrochloride sublingual film (Suboxone®; no generics):* Available as a film in doses of buprenorphine/ naloxone of 2mg/0.5mg, 4mg/1 mg, 8mg/2 mg and 12mg/3 mg. Tablet formulations are available as 2mg/0.5mg and 8mg/2mgs. Discontinuation of branded Suboxone sublingual tablets is to occur on 3/18/13, being replaced by the sublingual film described above. *Buprenorphine transdermal system (Butrans®; no generics):* FDA-approved for moderate to severe chronic pain. Available as transdermal patches at 5mcg/hr, 10mcg/hr and 20mcg/hr. See also Buprenorphine for treatment of opioid dependence.
Buprenorphine for opioid dependence	Recommended for selected patients for treatment of opioid dependence. The use of buprenorphine maintenance therapy was introduced in 2002. This drug can be prescribed in a physician office setting for this indication by certified physicians. Original studies investigate the use of buprenorphine for treatment of heroin addiction and research is still ongoing for use in populations with prescription drug abuse, or with comorbid dependency and chronic pain. *Drug characteristics in terms of dependence and addiction treatment:* The drug is a semi-synthetic mu opioid partial agonist and a kappa receptor antagonist. The medication as used for this indication is available in sublingual tablet or film formulations. Current literature indicates many of

	the drug's effects plateau at 16 mg, although doses of 32 mg are used clinically. Most patients stabilize at doses between 16 and 24 mg given in a once daily dose. The intensity of the rewarding effect is milder and plateaus at higher doses, and these characteristics are thought to limit abuse potential. (Alford, 2011) (Clark, 2011) (Weiss, 2011) (Bart, 2012) (Ducharme, 2012) (Mark, 2012) (Colson, 2012) Zubsolv (buprenorphine and naloxone), a recently FDA-approved medication for maintenance treatment of opioid dependence, is a once-daily sublingual tablet that offers higher bioavailability that allows patients to use lower strength and reduce the amount of available drug for potential misuse and diversion. (FDA, 2013) See also Buprenorphine for treatment of chronic pain.
Bupropion (Wellbutrin®)	Recommended as an option after other agents. Bupropion has shown some efficacy in neuropathic 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 specific Bupropion listing in section on Antidepressants for chronic pain for more information and references.
Butrans™ (buprenorphine)	See Buprenorphine.
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 an 8 week period) produced improvements in pain, pressure tolerance and joint moblity. (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 for pain. A growing number of states (23 at the time of publication of this guideline) (NCSL, 2013) have approved the use of medical marijuana for the treatment of chronic pain, but there are no quality studies supporting cannabinoid use, and there are serious risks. 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 that mid-range doses provided some pain relief, but high doses appeared to exacerbate pain. (Wallace, 2007) Cannabis use is 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 pain, especially in instances in which learning and memory are integral to a patient's work and lifestyle. (Wilsey, 2008) Cannabinoids

	as analgesic agents can have an undesirable CNS impact, and, in many cases, dose optimization may not be realizable before onset of excessive side effects. (McCarberg, 2007) This study concluded that nabilone, a synthetic cannabinoid approved for treatment of severe nausea and vomiting associated with cancer chemotherapy, may be a useful addition to pain management and should be further evaluated in randomized controlled trials. (Berlach, 2006) See also Nabilone (Cesamet®). The results of this preliminary study suggest that dronabinol, a synthetic THC, resulted in additional analgesia among patients taking opioids for chronic noncancer pain. (Narang, 2008) Adding a cannabinoid to opioid therapy may lead to greater pain relief at lower opioid doses, according to a new study, but more study is needed. (Abrams, 2011) *Recent research:* Cannabis users who start using the drug as adolescents show an irreparable decline in IQ, with more persistent use linked to a greater decline, according to a New Zealand prospective study with over 1,000 patients. Adolescents are particularly vulnerable to developing cognitive impairment from cannabis and the drug, far from being harmless, as many teens and even adults believe, can have severe neurotoxic effects on the brain. Between the ages of 8 and 38 years, individuals who began using cannabis in adolescence and continued to use it for years thereafter lost an average of 8 IQ points, versus rising slightly in nonusers. Cessation of cannabis did not restore IQ among teen-onset cannabis users. Cannabis in New Zealand has a THC content of approximately 9%. (Meier, 2013) The American Society of Addiction Medicine (ASAM) has taken a position against medical marijuana, saying physicians should not recommend that patients use marijuana for medical purposes, because it is a dangerous, addictive drug and is not approved by the FDA. Cannabis is unstable and unpredictable and the drug should be subject to the same standards that apply to other medications. For every disease and disorder for which marijuana has been recommended, there is a better, FDA-approved medication. (Gitlow, 2013) An RCT of smoked marijuana and oral dronabinol (tetrahydrocannabinol; THC) showed that both produce an analgesic effect, but this effect lasts longer with dronabinol, and it is less subject to abuse. Reported advantages to smoked marijuana are its faster onset and the relative ease with which doses can be managed, but it is not always safe or feasible to smoke marijuana. In addition to the cardiopulmonary risks this carries, smoking anything is not acceptable, such as on an airplane or at work. On the other hand, dronabinol is not approved for pain, only for chemotherapy-induced nausea and AIDS-related weight loss. And, the recommended doses (2.5 mg to 5 mg) are much lower than those used in this study (10 mg to 20 mg) that seemed to have an effect on pain. (Cooper, 2013) The 2 main chemical ingredients in marijuana, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), can have very different effects on behavior and in the brain, this research shows. Even a single modest dose of THC, the main ingredient in marijuana that is responsible for the high, can induce psychotic symptoms, whereas CBD can be useful as a treatment for psychosis. Regular marijuana use in vulnerable individuals is associated with increased risk of developing psychotic disorders such as schizophrenia, in which patients lose contact with reality. CBD, on the other hand, had the opposite effect,

	increasing the response of the left caudate, an area of the brain weakened by THC. (Bhattacharyya, 2012) Long-term marijuana use has been linked to structural brain changes similar to those observed in schizophrenia patients, and they correlate with poorer working memory. Teens who smoked marijuana daily for about 3 years performed poorly on tests of working memory and had abnormal changes in brain structures akin to those seen in patients with schizophrenia, linking long-term use of marijuana to brain abnormalities that appear to last for at least a few years after people stop using it. (Smith, 2013) *Epilepsy:* Cannabinoids have therapeutic potential in epilepsy, but their efficacy and safety remain to be proven. There are no controlled trials demonstrating that marijuana is safe or effective for the treatment of epilepsy. On the other hand, there is evidence that marijuana may be harmful, particularly in the developing brain after regular use. Synthetic cannabinoids appear even more toxic. For patients who have exhausted conventional therapies, medical marijuana, with anecdotal evidence of seizure control, could be considered as an alternative therapy. Such use should be carefully monitored by a physician. (Robson, 2014)
Capsaicin, topical (chili pepper/ cayenne pepper)	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 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. Topical OTC pain relievers that contain menthol,

	methyl salicylate, or capsaicin, may in rare instances cause serious burns, a new alert from the FDA warns. (FDA, 2012) See also CRPS, medications; Diabetic neuropathy; & 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 FDA-approved for symptomatic relief of discomfort associated with acute pain in musculoskeletal conditions as an adjunct to rest and physical therapy. (AHFS, 2008) 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). As of January 2012, carisoprodol is scheduled by the DEA as a Schedule IV medication. (DEA, 2012) It has been suggested that the main effect is due to generalized sedation and treatment of anxiety. *Beers criteria:* The AGS updated Beers criteria for inappropriate medication use includes carisoprodol. This is a list of potentially inappropriate medications for older adults. (AGS, 2012) *Abuse:* 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) (Owens, 2007) (Reeves, 2012) There was a 300% increase in numbers of emergency room episodes related to carisoprodol from 1994 to 2005. (DHSS, 2005) Hospital emergency department visits involving the misuse of carisoprodol have doubled over five years, study shows. (SAMHSA, 2011) *Intoxication signs:* 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) *Withdrawal:* 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, 2010) (Reeves, 2007) (Reeves, 2004) *Weaning:* 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, carisoprodol (Soma®).

Catapres® (Clonidine)	See Clonidine, intrathecal.
Causality (determination)	Recommend determination of causation typically involving mechanism of injury, temporal relationship, and dose effect. See specific body-part chapters in the MTUS.
Celebrex® (celecoxib)	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.
Celecoxib (Celebrex®)	See Celebrex® above. See also NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Celecoxib (Celebrex®) listing for more information and references. A large systematic review of available evidence on NSAIDs confirms that naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk. Celecoxib (Celebrex), on the whole, had a slightly increased risk of cardiovascular events at low and high doses, although there were few studies testing doses >200 mg/day. Celecoxib, especially at doses >400 mg/day, should be avoided in patients at high risk of cardiovascular disease. (McGettigan, 2011)
Cellulitis treatment	Recommended as indicated below. Cellulitis is a common, potentially serious bacterial skin infection, entering the skin usually via a cut or abrasion. The lower legs are most commonly affected, but cellulitis can occur anywhere on the body. Staphylococcus and streptococcus bacteria are the most common causes of cellulitis. Oral antibiotics are effective in over 90% of patients, but almost all abscesses require drainage for resolution, regardless of the microbiology of the infection. A peripherally inserted central catheter (PICC line), a form of intravenous access that can be used for a prolonged period of time for extended antibiotic therapy, may be required. Urgent consultation with a surgeon should be sought in cases of crepitus, circumferential cellulitis, necrotic-appearing skin, rapidly evolving cellulitis, pain disproportional to physical examination findings, severe pain on passive movement, or other clinical indications of necrotizing fasciitis. (Stevens, 2005) (Liu, 2011)
Cesamet®	See Nabilone.
Chi machine	Not recommended for chronic pain. May be used for lymphedema, but not recommended for other conditions, including chronic pain, since there is no evidence of its effectiveness.
Chiropractic treatment	See Manual therapy & manipulation.
Chlordiazepoxide	Not recommended. See Benzodiazepines.
Cholecalciferol	See Vitamin D.
Chondroitin sulfate	See Glucosamine (and Chondroitin Sulfate).

Chronic pain programs / (Functional restoration programs [FRPs])	Recommended where there is access to programs with proven successful outcomes (i.e., decreased pain and medication use, improved function and return to work, decreased utilization of the health care system), for patients with conditions that have resulted in "Delayed recovery." Also see Introduction to the MTUS Chronic Pain Guidelines. There should be evidence that a complete diagnostic assessment has been made, with a detailed treatment plan of how to address physiologic, psychological and sociologic components that are considered components of the patient's pain. Patients should show evidence of motivation to improve and return to work, and meet the patient selection criteria outlined below. While these programs are recommended (see criteria below), 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) 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) See Biopsychosocial model of chronic pain. ***Types of programs:*** There is no one universal definition of what comprises interdisciplinary/multidisciplinary treatment. These pain rehabilitation programs (as described below) combine multiple treatments, and at the least, include psychological care along with physical and/or occupational therapy (including an active exercise component as opposed to passive modalities). 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;and (e) education. ***Outcomes measured:*** Studies have generally evaluated variables such

	as pain relief, function and return to work. More recent research has begun to investigate the role of comorbid psychiatric and substance abuse problems in relation to treatment with pain programs. Recent literature has begun to suggest that an outcome of chronic pain programs may be to "demedicalize" treatment of a patient, and encourage them to take a more active role in their recovery. These studies use outcomes such as use of the medical care system post-treatment. The role of the increasing use of opioids and other medications (using data collected over the past decade) on outcomes of functional restoration is in the early stages, and it is not clear how changes in medication management have affected outcomes, if at all. See MTUS Opioids Treatment Guidelines for recommendations on the use of opioids. Also see specific body-part chapters in the MTUS. *Multidisciplinary back training:* (involvement of psychologists, physiotherapists, occupational therapists, and/or medical specialists). The training program is partly based on physical training and partly on behavioral cognitive training. Physical training is performed according to the "graded activity" principle. The main goal is to restore daily function. A recent review of randomized controlled studies of at least a year's duration found that this treatment modality produced a positive effect on work participation and possibly on quality of life. There was no long-term effect on experienced pain or functional status (this result may be secondary to the instrument used for outcome measure). Intensity of training had no substantial influence on the effectiveness of the treatment. (van Geen, 2007) (Bendix, 1997) (Bendix, 1998) (Bendix2, 1998) (Bendix, 2000) (Frost, 1998) (Harkapaa, 1990) (Skouen, 2002) (Mellin, 1990) (Haldorsen, 2002) *Intensive multidisciplinary rehabilitation of chronic low back pain:* The most recent Cochrane study was withdrawn from the Cochrane (3/06) as the last literature search was performed in 1998. Studies selected included a physical dimension treatment and at least one other treatment. ***Role of opioid use:*** See MTUS Opioids Treatment Guidelines for recommendations on the use of opioids. ***Role of comorbid psychiatric illness:*** Comorbid conditions, including psychopathology, should be recognized as they can affect the course of chronic pain treatment. In a recent analysis, patients with panic disorder, antisocial personality disorder and dependent personality disorder were > 2 times more likely to not complete an interdisciplinary program. Personality disorders in particular appear to hamper the ability to successfully complete treatment. Patients diagnosed with post-traumatic stress disorder were 4.2 times more likely to have additional surgeries to the original site of injury. (Dersh, 2007) The prevalence of depression and anxiety in patients with chronic pain is similar. Cohort studies indicate that the added morbidity of depression and anxiety with chronic pain is more strongly associated with severe pain and greater disability. (Poleshuck, 2009) (Bair, 2008) ***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) There is need for research in terms of necessity and/or effectiveness of counseling for patients considered to be "at-risk" for post-discharge problems. (Proctor, 2004) 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) increased duration of pre-referral disability time; (8) higher prevalence of opioid use; and (9) elevated pre-treatment levels of pain. (Linton, 2001) (Bendix, 1998) (McGeary, 2006) (McGeary, 2004) (Gatchel2, 2005) (Dersh, 2007) ***Role of duration of disability:*** There is little research as to the success of return to work with functional restoration programs in long-term disabled patients (> 24 months). *Studies supporting programs for patients with long-term disability:* Long-term disabled patients (at least 18 months) vs. short-term disabled (4 to 8 months) were evaluated using Pride data (1990-1993). No control was given for patients that did not undergo a program. During the time studied program dropouts averaged 8% to 12%. (It does appear that at the time of this study, participants in the program were detoxified from opioids prior to beginning.) The long-term disabled group was more likely to have undergone spinal surgery, with this likelihood increasing with time. Return to work was statistically different between the short-term disabled (93%) and the long-term disabled-18 months (80%). The long-term disabled-24 months group had a 75% return to work. Long-term disabled-18 month patients were statistically more likely to visit new health providers than short-term disabled patients (34% and 25% respectively). Work retention at one year in groups up to 24 months duration of disability was 80%. This dropped to 66% in the group that had been disabled for > 24 months. The percentage of recurrent lost time injury claims increased from around 1% in the groups disabled for < 35 months to 8.3% in the groups disabled for > 36 months. A main criterion for success appeared to be the decision of the patient to actively participate in the program rehabilitation goals. (Jordan, 1998) *Studies suggesting limited results in patients with long-term disability:* While early studies have suggested that time out-of-work is a predictor of success for occupational outcomes, these studies have flaws when an attempt is made to apply them to chronic pain programs. (Gallagher, 1989) (Beals, 1972) (Krause, 1994) Washington State studied the role of duration of work injury on outcome using a statistical model that allowed for a comparison of patients that participated in a multidisciplinary pain program (using data from 1991-1993) vs. those that were evaluated and not treated. This was not an actual study of time of disability, but of duration of injury (mean years from injury to evaluation of 2.6 years for the treated group and 4.0 years for the evaluated only group). The original statistical analysis allowed for a patient to be included in a "treated group" for those

	individuals that both completed and did not complete the program. Data was collected from 10 sites. Each of the centers was CARF approved and included Pysch/behavioral treatment, vocation counseling and physical therapy. A sub-study evaluated a comparison of patients that were treatment completers vs. those that did not participate (78.6%, N-=963). No information was given in terms of surgical procedures or medications. The primary outcome was time loss status of subjects 2 years after they had undergone the index pain center evaluation. In the 2001 study, if chronicity of duration of injury was controlled for, there was no significant benefit produced in terms of patients that were receiving time-loss benefits at 2-years post treatment between the two groups. Approximately 60% of both groups were not receiving benefits at the two-year period. As noted, the "treated patient" was only guaranteed to have started a program. A repeat analysis of only the patients who completed the study did not significantly change the results of the study. In a 2004 survey follow-up no significant difference was found between treated and untreated groups, although the treated group had better response. The survey response was 50%, and the treatment responders were more likely to be disabled at the time of the survey. The authors suggest that the results indicated early intervention was a key to response of the programs, and that modest goals (improvement, not cure) be introduced. (Robinson, 2004) (Robinson, 2001) [The authors also concluded that there was no evidence that pain center treatment affects either disability status or clinical status of injured workers.] ***Timing of use****:* Intervention as early as 3 to 6 months post-injury may be recommended depending on identification of patients that may benefit from a multidisciplinary approach (from programs with documented positive outcomes). See Chronic pain programs, early intervention. ***Role of post-treatment care (as an outcome):*** Three variables are usually examined; (1) New surgery at the involved anatomic site or area; (2) Percentage of patients seeking care from a new provider; (3) Number of visits to the new provider over and above visits with the health-care professional overseeing treatment. It is suggested that a "new provider" is more likely to reorder diagnostic tests, provide invasive procedures, and start long-term analgesics. In a study to determine the relationship between post-treatment healthcare-seeking behaviors and poorer outcomes (using prospectively analyzed PRIDE data on patients with work-related musculoskeletal injuries), patients were compared that accessed healthcare with a new provider following functional restoration program completion (approximately 25%) to those that did not. The former group was significantly more likely to have an attorney involved with their case (22.7% vs. 17.1%, respectively), and to have had pre-rehabilitation surgery (20.7% vs. 12.1%, respectively). Return to work was higher in the group that did not access a new provider (90% vs. 77.6% in the group that did access). The group that did not access new providers also was more likely to be working at one year (88% vs. 62.2% in the group that accessed new providers). It should be noted that 18% of the patients that entered the program dropped out or were asked to leave. The authors suggested monitoring of additional access of healthcare over and above that suggested at the end of the program, with intervention if needed. (Proctor,

	2004) The latest AHRQ Comparative Effectiveness Research supports the ODG recommendations. (AHRQ, 2011) See also Chronic pain programs, intensity; Chronic pain programs, opioids; Functional restoration programs; Chronic pain programs, early intervention; Progressive goal attainment program (PGAP™). **Criteria for the general use of multidisciplinary pain management programs:** Outpatient pain rehabilitation programs may be considered medically necessary in the following circumstances: (1) The patient has a chronic pain syndrome, with evidence of loss of function that persists beyond three months and has evidence of three or more of the following: (a) Excessive dependence on health-care providers, spouse, or family; (b) Secondary physical deconditioning due to disuse and/or fear-avoidance of physical activity due to pain; (c) Withdrawal from social activities or normal contact with others, including work, recreation, or other social contacts; (d) Failure to restore preinjury function after a period of disability such that the physical capacity is insufficient to pursue work, family, or recreational needs; (e) Development of psychosocial sequelae that limits function or recovery after the initial incident, including anxiety, fear-avoidance, depression, sleep disorders, or nonorganic illness behaviors (with a reasonable probability to respond to treatment intervention); (f) The diagnosis is not primarily a personality disorder or psychological condition without a physical component; (g) There is evidence of continued use of prescription pain medications (particularly those that may result in tolerance, dependence or abuse) without evidence of improvement in pain or function. (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) An adequate and thorough multidisciplinary evaluation has been made. This should include pertinent validated diagnostic testing that addresses the following: (a) A physical exam that rules out conditions that require treatment prior to initiating the program. All diagnostic procedures necessary to rule out treatable pathology, including imaging studies and invasive injections (used for diagnosis), should be completed prior to considering a patient a candidate for a program. The exception is diagnostic procedures that were repeatedly requested and not authorized. Although the primary emphasis is on the work-related injury, underlying non-work related pathology that contributes to pain and decreased function may need to be addressed and treated by a primary care physician prior to or coincident to starting treatment; (b) Evidence of a screening evaluation should be provided when addiction is present or strongly suspected; (c) Psychological testing using a validated instrument to identify pertinent areas that need to be addressed in the program (including but not limited to mood disorder, sleep disorder, relationship dysfunction, distorted beliefs about pain and disability, coping skills and/or locus of control regarding pain and medical care) or diagnoses that would better be addressed using other treatment should be performed; (d) An evaluation of social and vocational issues that require assessment. (4) If a goal of treatment is to prevent or avoid controversial or optional

	surgery, a trial of 10 visits (80 hours) may be implemented to assess whether surgery may be avoided. (5) If a primary reason for treatment in the program is addressing possible substance use issues, an evaluation with an addiction clinician may be indicated upon entering the program to establish the most appropriate treatment approach (pain program vs. substance dependence program). This must address evaluation of drug abuse or diversion (and prescribing drugs in a non-therapeutic manner). In this particular case, once drug abuse or diversion issues are addressed, a 10-day trial may help to establish a diagnosis, and determine if the patient is not better suited for treatment in a substance dependence program. Addiction consultation can be incorporated into a pain program. If there is indication that substance dependence may be a problem, there should be evidence that the program has the capability to address this type of pathology prior to approval. (6) Once the evaluation is completed, a treatment plan should be presented with specifics for treatment of identified problems, and outcomes that will be followed. (7) There should be documentation that the patient has motivation to change, and is willing to change their medication regimen (including decreasing or actually weaning substances known for dependence). There should also be some documentation that the patient is aware that successful treatment may change compensation and/or other secondary gains. In questionable cases, an opportunity for a brief treatment trial may improve assessment of patient motivation and/or willingness to decrease habituating medications. (8) Negative predictors of success (as outlined above) should be identified, and if present, the pre-program goals should indicate how these will be addressed. (9) If a program is planned for a patient that has been continuously disabled for greater than 24 months, the outcomes for the necessity of use should be clearly identified, as there is conflicting evidence that chronic pain programs provide return-to-work beyond this period. These other desirable types of outcomes include decreasing post-treatment care including medications, injections and surgery. This cautionary statement should not preclude patients off work for over two years from being admitted to a multidisciplinary pain management program with demonstrated positive outcomes in this population. (10) Treatment is not suggested for longer than 2 weeks without evidence of compliance and significant 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 they are being made on a concurrent basis. (11) Integrative summary reports that include treatment goals, compliance, progress assessment with objective measures and stage of treatment, must be made available upon request at least on a bi-weekly basis during the course of the treatment program. (12) Total treatment duration should generally not exceed 4 weeks (20

	full-days or 160 hours), (or the equivalent in part-day sessions if required by part-time work, transportation, childcare, or comorbidities). (Sanders, 2005) If treatment in excess of 4 weeks is required, a clear rationale for the specified extension and reasonable goals to be achieved should be provided. Longer durations require individualized care plans explaining why improvements cannot be achieved without an extension as well as evidence of documented improved outcomes from the facility (particularly in terms of the specific outcomes that are to be addressed). (13) At the conclusion and subsequently, neither re-enrollment in repetition of the same or similar rehabilitation program (e.g. work hardening, work conditioning, out-patient medical rehabilitation) is medically warranted for the same condition or injury (with possible exception for a medically necessary organized detox program). Prior to entry into a program the evaluation should clearly indicate the necessity for the type of program required, and providers should determine upfront which program their patients would benefit more from. A chronic pain program should not be considered a "stepping stone" after less intensive programs, but prior participation in a work conditioning or work hardening program does not preclude an opportunity for entering a chronic pain program if otherwise indicated. (14) Suggestions for treatment post-program should be well documented and provided to the referral physician. The patient may require time-limited, less intensive post-treatment with the program itself. Defined goals for these interventions and planned duration should be specified. (15) Post-treatment medication management is particularly important. Patients that have been identified as having substance abuse issues generally require some sort of continued addiction follow-up to avoid relapse. 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. If a primary focus is drug treatment, the initial evaluation should attempt to identify the most appropriate treatment plan (a drug treatment /detoxification approach vs. a multidisciplinary/interdisciplinary treatment program). See Chronic pain programs, opioids; Functional restoration programs. Also, see MTUS Opioids Treatment Guidelines" for recommendations on the use of multidisciplinary pain programs related to opioids.
Chronic pain programs, early	Recommended, based on identification of patients that may benefit from early intervention via a multidisciplinary approach, as indicated below. The

intervention	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) (Jordan, 1998) Some early intervention programs have been referred to as "secondary treatment," and differ from the more traditional, palliative care pain programs by not only the earlier onset of treatment, but by treatment intensity and level of medical supervision. (Mayer, 2003) *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) Risk factors are identified with available screening tools or 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 or evidence of work organizational factors limiting return to work without interventions. (f) Evidence of psychosocial barriers that make return to work unlikely. (g) Loss of employment or evidence of partial disability involving ability to perform only "part-time" work or work with "light-duty" restrictions for greater than 4 months. (Mayer, 2003) (Gatchel, 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.
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. Also see MTUS Opioids Treatment Guidelinesfor recommendations on the use of multidisciplinary pain programs. The limited research that is available indicates that daily opioid use, in low doses, does not decrease effectiveness of chronic pain programs, although outcomes may be less optimal for patients who continue to use opioids. (Dersh, 2008) Current research indicates that simultaneous dependency/addiction programs with pain programs are a viable option. Some patients will require treatment of addictive disease before pain management can be effectively addressed. Patients with opioid dependence may require additional, long-term follow-up after the rehabilitation program. Criteria for this follow-up are still under research. ***Programs that include detoxification as part of their protocol*** *PRIDE Program:* In 2008 the PRIDE program (Progressive Rehabilitation Institute of Dallas for Ergonomics) (Dersh 2008) evaluated the role of post-injury opioid-dependence disorder (ODD) to assess if prescription opioid dependence (assessed at the beginning of rehabilitation) affected treatment outcome in patients with chronic disabling occupational spinal disorders. All patients with opioid dependence exhibited a lack of improvement or worsening in psychological well-being and social and vocational functioning despite the clinician's best attempts at pain control. As noted, patients were required to taper off of all opioids early in treatment. Patients who had the following identified during initial treatment were referred to a facility psychiatrist (who had board certification in addiction): 1) evidence of use of high-dose/potency opioids or multiple opioids; 2) patients with a known history of current or lifetime substance-use disorders; 3) patients with known or easily apparent psychiatric disturbance; 4) patients that did not progress well in their detoxification under care of the attending physician. A diagnosis of substance dependence was made, in part, using the structured clinical interview for DSM-non-patient version (SCID-NP) and the SCID personality disorders (SCID-II). Prevalence of ODD was 15% on entering the program. ODD patients had greater length of disability (17 months for non-ODD vs. 29 months for ODD patients), were 2.5 times more likely to have had pretreatment surgery and 1.5 times more likely to be represented by an attorney. ODD patients were likely to have more axis I and II disorders (other than substance abuse disorders) than non-ODD patients. The odds ratio in ODD patients for current major depressive disorder was 1.7 and for current anxiety disorder was 1.7. ODD was significantly associated with preinjury substance-use disorders (O.R. 1.9). The substances identified included alcohol and drugs other than opioids. The axis II disorders associated with ODD were antisocial personality disorder and borderline personality disorder. *Results of program completers:* Program completion was not significantly different between ODD and non-ODD patients. The primary reason for non-completion was non-compliance and treatment refusal and failure to

develop a work plan. Only 5% of patients did not complete the program due to continued substance abuse/dependence. After adjusting for demographics and comorbid psychiatric disorders, opioid-dependent patients were 1.7 times less likely to return to work (95% confidence interval of this result was 1.0, 2.7, indicating a trend only). The opioid dependent patients were 2 times less likely to retain work at the 1-year interview (95% CI; 1.3, 3.0), and 1.7 times more likely to engage in healthcare utilization with new providers (95% CI; 1.2, 2.5). These rates were even higher when adjustment for comorbid psychiatric pathology was not made. (Dersh, 2007)

Detoxification and referral to an addiction specialist in this program: This program included detoxification from opioids early in the treatment program. Patients taking high-dose/potency opioids or multiple opioids, patients with a known history of current or lifetime substance-abuse disorders, patients with known or easily apparent psychiatric disturbance, and/or patients who did progress well with detoxification under care of the attending physician were referred to the facility psychiatrist (board certified in addiction). Patients that continued to use opioids were offered inpatient detoxification. If refused, they were discharged from the program.

Assessments utilized: Structured clinical interview for DSM-non-patient versions (SCID-NP) to assess for axis I psychiatric disorders such as schizophrenia, depression and substance-use disorders and the SCID personality disorders (SCID-II) to assess for axis-II DSM personality disorders (Borderline, Antisocial, Paranoid).

Programs that allow some opioid use

Mayo Clinic Pain Rehabilitation Program: This program also incorporates simultaneous opioid withdrawal and pain rehabilitation. The original study by Rome et al. was designed to (1) evaluate the frequency of maintenance opioid therapy in the population admitted to the multidisciplinary program, (2) compare demographic characteristics, pain severity, emotional distress, and level of function of patients taking maintenance opioids at admission vs. those who were not, (3) compare outcomes of the two groups (pain severity, interference with pain, perceived life control, affective distress, general activity level, depression, and catastrophizing). Research (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. They also had higher scores for depression. Over one-half of patients took opioids at the time of admission (57.1%). The majority of patients completed the program (91%). At the completion of treatment 13.9% of patients were still taking opioids (mean oral morphine equivalents a day of 67.6 mg/day). Significant improvement was found for all outcome variables immediately after completion of the program and at 6-months post-treatment regardless of opioid status at admission. In this program, there was no difference between opioid and non-opioid groups upon discharge or at six-months of follow-up, post-treatment. The conclusion of the researchers was that opioid withdrawal did not prohibit rehabilitation gains. (Rome, 2004)

Specific Evaluation Studies: A specific assessment of the use of opioids on

	treatment outcomes was undertaken by Townsend et al. (Townsend 2008) On admission, patients taking low- and high-dose opioids reported significantly greater pain severity and depression than those patients that were not taking this class of medication. Regardless of opioid status on admission, significant improvement was found for all outcomes following treatment and at six-months post treatment (as listed above and as measured using the instruments listed below in "assessments utilized"). Crisostomo et al evaluated patients in terms of three specific groups based on history of spinal surgery: fusion; non-fusion; and no surgical procedure. They found that patients that had undergone surgery were more likely to be taking opioids on admission (chi-square=8.92, P= 0.012, fusion 65.2%, nonfusion = 70%, no-surgery group = 48.4%). Pain severity and duration was highest in the fusion group. Patients that had undergone fusion were slightly more likely to drop out of the program (chisq=5.94, P=0.051; completers in the fusion group =78%, nonfusion group = 89%, and no-surgery group = 87%). Regardless of surgical status, patients showed significant and nearly equal improvement. In terms of medications the overall decrease in opioid use was 78.6%. Benzodiapezine decrease was 39.9%. The only significant difference in medication use at dismissal was for benzodiazepines, with more surgery patients using this class of drugs (chisq= 6.62, P = 0.037, fusion = 21.1%, nonfusion = 20.5%, no surgery = 9.6%). (Crisostomo 2008) Overall, successful opioid withdrawal and treatment completion was found for patients that had had lumbar spine surgery. *Assessments utilized:* Multi-dimensional Pain Inventory (MPI); SF-36; Center for Epidemiologic Studies-Depression Scale (CES-D); Pain catastrophizing scale (PCS). ***Programs that do not 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.
Citalopram	See SSRIs (selective serotonin reuptake inhibitors).
Clonazepam	Not recommended. See Benzodiazepines.
Clonidine, intrathecal	Not recommended except as an end-stage treatment alternative for selected patients for specific conditions, and 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 on its own 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 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)
Clorazepate	Not recommended. See Benzodiazepines.
Codeine (Tylenol with Codeine®)	See MTUS Opioids Treatment Guidelines, Appendix F1, for dosing recommendations. Codeine is a schedule C-II controlled substance, but codeine with acetaminophen is a C-III 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 moderate to severe pain. Codeine has disadvantages in that it is a pro drug that needs to be converted by the cytochrome P450 isoenzyme 2D6 to morphine, plus there are FDA alerts of ultra-rapid metabolism. (Ray, 2013) See also specific Codeine (Tylenol with Codeine®) listing for more information and references. *Adverse effects:* Common effects include CNS depression and hypotension. Drowsiness and constipation occur in > 10% of cases. Codeine should be used in 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 sections on Behavioral interventions/ Cognitive Behavioral Therapy (CBT), Pyschological treatment , and Multi-disciplinary pain programs.
Cold lasers	See Low level laser therapy (LLLT).
Comorbid psychiatric disorders	Recommend screening for psychiatric disorders for patients with chronic unexplained pain, delayed recovery, poor response to treatment. Comorbid psychiatric disorders commonly occur in chronic pain patients. In a study of chronic disabling occupational spinal disorders in a large tertiary referral center, the overall prevalence of psychiatric disorders was 65% (not including pain disorder) compared to 15% in the general population. These included major depressive disorder (56%), substance abuse disorder (14%), anxiety disorders (11%), and axis II personality disorders (70%). (Dersh, 2006) When examined more specifically in an earlier study, results showed that 83% of major depression cases and 90% of opioid abuse cases developed after the musculoskeletal injury. On the other hand, 74% of substance abuse disorders and most anxiety disorders developed before the injury. This topic was also studied using the National Comorbidity Survey Replication (NCS-R), a national face-to-face household survey. (Dersh, 2002) See also Psychological evaluations.
Complex regional	See CRPS (complex regional pain syndrome).

pain syndrome (CRPS)	
Compound drugs	Not recommended as a first-line therapy. In general, commercially available, FDA-approved drugs should be given an adequate trial. If these are found to be ineffective or are contraindicated in individual patients, compound drugs that use FDA-approved ingredients may be considered. (Wynn, 2011) See specific entries for each ingredient. See also Topical analgesics, compounded. Pharmacy compounding has traditionally involved combining drug ingredients to meet the needs of specific patients for medications that are not otherwise commercially available, and it is undertaken on a patient-by-patient basis for patients who, for example, might be allergic to inactive ingredients in FDA-approved drugs or may need a different dosage strength or route of administration. Unlike commercially available drugs, these products are not approved by the FDA but rather are regulated by the state pharmacy board and state law governing the practice of pharmacy. The FDA does not regulate pharmacy-compounded products in recognition of the important public health function performed by traditional compounding. Recently, some pharmacies have been making and marketing stock compound drugs for the WC patient population. Among the FDA "Red Flags" for Enforcement Action on Compounded Drugs is: "Compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to amounts compounded after receiving valid prescriptions." (FDA, 2011) Compound topical analgesics may provide relief by acting locally over the painful site with lower risk of systemic adverse effects on the gastrointestinal system and drug interactions than oral NSAIDs. The issues surrounding compound drugs are due to uncertainties regarding whether the products are medically appropriate and whether payments are reasonable, with the latter issue possibly also involving who dispenses the drug. Medical necessity should be based on the patient's needs combined with the medical and scientific evidence presented in ODG. See also Co-pack drugs; Medical foods; Physician-dispensed drugs; Repackaged drugs; & Topical analgesics, compounded. **Criteria for Compound drugs:** (1) Include at least one drug substance (or active ingredient) that is the sole active ingredient in an FDA-approved prescription drug, not including OTC drugs. (2) Include only bulk ingredients that are components of FDA-approved drugs that have been made in an FDA-registered facility and have an NDC code. (3) Is not a drug that was withdrawn or removed from the market for safety reasons. (4) Is not a copy of a commercially available FDA-approved drug product. (5) Include only drug substances that have been supported as safe and

	effective for the prescribed indication by the FDA-approval process and/or by adequate medical and scientific evidence in the medical literature. This would allow off-label usage when supported by medical evidence. See specific entries for each ingredient in ODG for the medical and scientific evidence. See also Topical analgesics, compounded. (Wynn, 2011) (6) Any compounded product that contains at least one drug (or drug class) that is not recommended is not recommended. The use of compounded agents requires knowledge of the specific analgesic effect of each agent and how it will be useful for the specific therapeutic goal required. See also Topical analgesics, compounded. (Wynn, 2011)
Compounded topical analgesics	See Topical analgesics, compounded.
Constipation	See Opioid-induced constipation treatment.
ConZip (tramadol ER)	See MTUS Opioids Treatment Guidelines for guidance on the use of opioids in general.
Co-pack drugs	Co-packs are convenience packaging of a medical food product and a generic drug into a single package that requires a prescription. There is no evidence to support the medical necessity of co-packs, as there are no high-quality medical studies to evaluate co-packs on patient outcomes. Labelers may create a new NDC for the co-pack. While the generic drug is FDA-approved, the co-pack of a medical food and FDA-approved drug is not unless the manufacturer obtains FDA approval for the product as a new drug. See specific entries for each ingredient in ODG. See also Compound drugs; Medical foods; Physician-dispensed drugs; Repackaged drugs.
Corticosteroids	See Oral corticosteroids; Injection with anesthetics and/or steroids.
CRPS (complex regional pain syndrome)	See CRPS, pathophysiology (clinical presentation & diagnostic criteria); CRPS, diagnostic tests; CRPS, treatment; CRPS, sympathetic blocks (therapeutic); CRPS, medications.
CRPS, diagnostic criteria	See CRPS, pathophysiology (clinical presentation & diagnostic criteria).
CRPS, diagnostic tests	Recommend assessment of clinical findings as the most useful method of establishing the diagnosis. See CRPS, pathophysiology (clinical presentation & diagnostic criteria). Specific procedures are not generally recommended, except as indicated below. A gold standard for diagnosis of CRPS has not been established and no test has been proven to diagnose this condition. Assessment of clinical findings is currently suggested as the most useful method of establishing the diagnosis. The following procedures have been suggested for use as additional tools for diagnosis, with use based on the patient's medical presentation. Recent CRPS guidelines do not discuss these tests in general but general information is available at the Reflex Sympathetic Dystrophy Syndrome Association website. (Aker, 2008) (Harden, 2013) ***Imaging studies*** *Triple-phase bone scans (three-phase bone scintigraphy or TPBS):* Recommended for select patients in early stages to help in confirmation of the diagnosis. Routine use is not recommended. The three phases are

	referred to as blood flow (first phase injection), blood pool (second phase at approx 2 minutes post injection), and delayed (third phase at approx 3 hours). The diagnosis is suggested when the blood flow and blood pool images show diffuse asymmetric uptake, or when the delayed image indicates increased asymmetric periarticular uptake. There is research to suggest that the delayed phase is the most sensitive for the diagnosis. (Pankaj, 2006) (Wüppenhorst, 2010) Osteoporosis is seen at a later duration after the diagnosis is made. A positive test is not necessarily concordant with the presence or absence of CRPS I and the diagnostic value of a positive test for CRPS is considered low from the view point of the Budapest research criteria versus previously used criteria that were less restrictive. (Moon 2012) (Ringer, 2012) (Lee, 1995) Extremely variable levels of sensitivity are reported with use (in one case as low as 14%). (Schurmann 2007) The sensitivity of the test is less than its specificity and the former declines with increasing duration of CRPS. Suggestion has been made that TPBS it is most useful in the early duration after diagnosis (4-6 months). (Wüppenhorst, 2010) *Conditions in which similar findings are noted:* Similar findings can occur with the following pathology: immobilization; denervation; stroke; venous, arterial and/or lymphatic obstruction; and cellulitis. There is also a report of increased articular uptake produced by self-application of a tourniquet on the wrist with resolution of symptoms once a diagnosis of Munchausen's syndrome was made. (Rodriguez-Moreno, 1990) According to the ODG UR Advisor, CPT 78315, 3 phase bone imaging, had a WC Frequency of 23.47% for ICD9 code 337.2, Reflex sympathetic dystrophy (CRPS I), and a WC Frequency of 7.84% for ICD9 code 355, Mononeuritis of lower limb (CRPS II). (ODG-UR, 2011) *MRI:* Not specifically recommended for the diagnosis of CRPS due to low specificity of findings. CRPS findings in hand pathology include bone marrow edema of the carpals, skin edema, uptake of the skin, joint effusion and intraarticular uptake. (Schurmann, 2007) *Plain film x-rays:* Not specifically recommended for the diagnosis of CRPS alone. CRPS findings include soft tissue swelling, osteopenia/osteoporosis (generally patchy earlier in the disease and more generalized at a later duration), cortical bone resorption and articular erosion. These findings can also be seen with disuse atrophy. Radiographic findings are not considered a screening procedure as changes appear later in the disease, and findings may be seen in other conditions. X-rays of both extremities should be performed for comparison. The procedure may be most useful to evaluate for missed fractures. (Cappello 2012) ***Temperature measures***: Temperature differences are dynamic in patients with CRPS due to variables such as intraindividual shifts, with a measure at a single point of time producing an almost random result (in terms of whether the affected limb will be warmer or colder than the non-affected extremity). Skin temperature also appears to be affected by duration of disease, with some research suggesting that the affected extremity is warmer in early stages. Caution is advised since environmental conditions can affect test results. An additional problem is that temperature (and color) changes can be produced with short-term dependency, immobility and vascular or vasomotor diseases. With the addition of cold water

	immersion at 15 degrees C for 15 minutes the submerged hand remains cooler at 60 minutes. (Wasner, 2001) (Wasner, 2002) (Wasner, 2010) (Singh, 2006) (Marinus, 2011) Skin temperature can be measured using a contact method, although this can be painful. *Infrared thermometry:* Recommended in select patients for objective measure of temperature difference. Sensitivity is poor with better specificity. (Sherman , 1994) *Infrared thermography:* Not recommended. There is insufficient evidence to support the routine use of thermography for diagnosis of CRPS. (Krumova , 2008) (Schürmann, 2007) *Laser Doppler flowmetry:* Not recommended. Use is primarily for research and there is insufficient evidence to support routine clinical use. (Murray, 2004) (Aker, 2008) ***Sudomotor measures:*** Most formal diagnostic tests for this are laboratory based and not generally recommended. Tests include (1) the iontophoretic quantitative sudomotor axon reflex test (QSART), (2) the sialastic sweat imprint method, (3) the thermoregulatory sweat test (TST), (4) sympathetic skin response and related electrodermal activity, (5) sympathetic skin resistance and selective tissue conductance, (6) quantitative sensory testing (QST), (7) resting sweat output (RSO). ***Nerve conduction velocity:*** Can be considered as recommended to investigate the presence of nerve injury/ neuropathy and differentiate between CRPS I and II. (Aker, 2008) ***Tests considered experimental and not recommended:*** (1) Phentolamine injection; (2) Bone density testing; (3) Positron emission tomography (PET); (4) Single photon emission tomography (SPECT). ***Skin biopsy for evidence of small nerve fiber degeneration:*** Not recommended. While small nerve fiber pathology has been a causal factor for CRPS, this remains to be established. It should also be noted that other causes of neuropathic pain are frequently associated with loss of C-fiber peripheral terminals, making the specificity of these tests with respect to CRPS questionable. Common causes of small fiber polyneuropathy include diabetes, hematological malignancies, autoimmune conditions, infections, toxins (including medications) and mutations. Oaklander et al. have indicated this test is not promising for routine clinical analysis. (Devigilli, 2008) (Oaklander, 2006) (Marinus, 2011) (Oaklander, 2013) ***Sympathetic nerve blocks, diagnostic:*** Recommended in a limited role for diagnosis of sympathetically mediated pain with the understanding that sympathetic blocks are not specific for CRPS. See Sympathetically maintained pain (SMP). Less than 1/3 of patients with CRPS are likely to respond to sympathetic blockade. There are no signs or symptoms to predict block success. The use of sympathetic blocks for diagnostic purposes in CRPS I is based on previous hypotheses concerning involvement of the sympathetic nervous system as a pathophysiologic cause of this disease. Monitoring for sympathetic and sensory function after the block is required. In the upper extremity interpretation of up to 73% of blocks cannot be made due to compounding factors. (Krumova, 2011) (Schürmann, 2001) *Interpretation:* A current suggestion of adequate block is one that demonstrates an adequate and sustained increase in skin temperature (≥

	1.5° C and ≥ 90 minutes), without evidence of thermal or tactile sensory blocks. (Krumova, 2011) (Schürmann, 2001) An assessment for false-positives (unintentional sensory blocks) and false-negatives (insufficient sympathetic block) should be made. See also CRPS, sympathetic blocks (therapeutic). **Recommendations (based on consensus guidelines) for an adequate CRPS evaluation** (1) There should be evidence that the Budapest (Hardin) criteria have been evaluated for and fulfilled. (2) There should be evidence that all other diagnoses have been ruled out. A diagnosis of CRPS should not be accepted without a documented and complete differential diagnostic process completed as a part of the record. (3) If a sympathetic block is utilized for diagnosis, there should be evidence that this block fulfills criteria for success including that skin temperature after the block shows sustained increase (≥ 1.5° C and/or an increase in temperature to > 34° C) without evidence of thermal or tactile sensory block. Evidence of a Horner's response to upper extremity blocks should be documented. The use of sedation with the block can influence results, and this should be noted. (Krumova, 2011) (Schürmann, 2001)
CRPS, ketamine subanesthetic infusion	Not recommended. See Ketamine.
CRPS, medications	Recommended only as indicated below. Most medications have limited effectiveness, and recommendations are primarily based on extrapolation from neuropathic pain medication guidelines. A reason given for the paucity of medication studies is the absence of a gold-standard diagnostic test for CRPS and lack of uniformly accepted diagnostic criteria. (Ribbers, 2003) (Quisel2, 2005) (Harden, 2013) 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 earlier in the condition when positive response is obtained with sympathetic blocks. NSAIDs are recommended but no trials have shown effectiveness in CRPS-I, and they are recommended primarily in early or very late stages. (Stanton-Hicks, 2004) (Sharma, 2006) Because long-term controlled studies have not been conducted, DMSO should be considered investigational and used only after other therapies have failed. (FDA, 2010) 2. Stimulus-independent pain: The use of antidepressants (primarily tricyclics and SNRIs), anticonvulsants (with the most support for gabapentin), and opioids has been primarily extrapolated based on use for other neuropathic pain disorders. There are no long-term studies demonstrating efficacy of opioids as treatment for CRPS. See Antidepressants for neuropathic pain; & Anticonvulsants for chronic pain; also, MTUS Opioids Treatment Guidelines . Current literature does not support the use of clonidine. (Hsu, 2009) (Harden, 2013). 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 recognized for their side effects. See Ketamine. 4. Sympathetically maintained pain (SMP): See IV regional sympathetic blocks (for RSD/CRPS); CRPS, sympathetic block (therapeutic); CRPS, treatment. 5. Treatment of bone resorption and resultant pain with bisphosphonate-type compounds and calcitonin. Bisphosphonates include alendronate, ibandronate, risedronate, zoledronate, etidronate, and pamidronate. There is no research on the newer longer-lasting drugs that are administered by periodic IV infusion (ibandronate, zoledronate and pamidronate). Significant improvement has been found in limited studies with 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. There has also been evidence of improvement of pain with pamidronate. Osteopenia was not an outcome. (Manicourt, 2004) See also Bisphosphonates. Mixed results have been found with intranasal calcitonin (Miacalcin®). (Sahin, 2005) (Appelboom, 2002) (Rowbathan, 2006) (Sharma, 2006) (Perez, 2001) The mechanism of action of these drugs is uncertain. 6. Treatment of dystonia: Oral baclofen is a first-line option. Benzodiazepines and long-term use of muscle relaxants such as cyclobenzaprine are not recommended. (Harden, 2013) 7. Treatment considered experimental and not recommended: IVIG, Sildenafil
CRPS, pathophysiology (clinical presentation & diagnostic criteria)	Recommend using a combination of criteria as per the revised Budapest (Harden) criteria as indicated below to make this diagnosis. There are no objective gold-standard diagnostic criteria for CRPS I or II. The diagnosis is based on what are predominately subjective criteria which are shared by many other diseases (see *Differential diagnosis* below). Current diagnostic criteria specifically indicate that there can be no other diagnosis that better explains signs and symptoms. The importance of establishing a correct diagnosis and to prevent potentially harmful and/ or unwarranted treatment cannot be emphasized enough. ***Pathophysiology:*** Multiple hypotheses have been promoted to explain both CRPS I and II. These include peripheral mechanisms that are inflammatory, altered cutaneous innervation after injury, peripheral sensitization, altered sympathetic and catecholaminergic function, altered somatosensory representation in the brain, genetic factors, central mechanisms, and psychophysiological interactions. Lab findings have included signs of increased neurogenic inflammation, small fiber neuropathy, tissue hypoxia and altered immune response. Most researchers feel that the interaction between these multiple pathways is what explains the heterogeneity of presentation and course. (Marinus, 2011) (Bruehl, 2010) The associations of non-dermatomal patterns of pain, unusual movement disorders and somatovisceral dysfunction have been particularly difficult to explain. In addition, the objective physical signs of CRPS, including imaging, can be created with disuse and or physical manipulation. (Cooper, 2013) (Bruehl, 2010) (Harden, 2013) (Goebel, 2012) (Rodriguez-Moreno, 1990)

	CRPS Criteria **A. CRPS-I (previously referred to as reflex sympathetic dystrophy RSD):** The three criteria generally identified in the literature include those suggested by Veldman et al., those originally suggested by the IASP, and a further modification of the latter referred to as the Budapest (Harden) criteria. Agreement between the three sets is poor, with the most frequent diagnoses made using the original IASP criteria and the lowest using the Budapest criteria. A major problem is that depending on the diagnostic criteria utilized, comparability of studies is compromised. The risk of misdiagnosis increases depending on the point of reference. Veldman Criteria: (1) At least four out of five signs or symptoms must be present (pain, difference in skin color, edema, difference in skin temperature and active range of motion); (2) Signs and symptoms are present in an area larger than might be expected of initial trauma; (3) An increase of signs and/or symptoms occur during or after exercise. (Veldman, 1993) The IASP (International Association for the Study of Pain) early on 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, often resulting in significant impairment of motor function, and showing variable progression over time. (Stanton-Hicks, 1995) Diagnostic criteria defined by IASP in 1994 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) The Budapest (Harden) Criteria represent a revision of the above IASP Criteria. There are two versions of these proposed diagnostic criteria. A *diagnostic version* was developed to maximize sensitivity (identify true positive cases) with adequate specificity (i.e. avoiding a false positive diagnosis). A *research version* was developed to more equally balance sensitivity and specificity. The *diagnostic criteria* are the following: (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) (Harden, 2010) This diagnostic version produces a sensitivity of 85% and specificity of 69%. The research version requires reporting of at least one symptom in *each of the four* categories (vs. in three of the four in the diagnostic version). This provides a sensitivity of 70% and specificity of 96%. (Harden, 2013) AMA Guidelines: This group puts a strong emphasis on the differential diagnostic process. They point out that there is no gold standard diagnostic feature which reliably distinguishes the diagnosis of CRPS for presentations that clearly are not CRPS. They state, "Scientific findings have actually indicated that whenever this diagnosis is made, it is probably incorrect." (AMA Guides, 6th ed.) Other authors have questioned the usefulness of diagnostic testing over and above history and physical findings. (Quisel, 2005) (Yung, 2003) (Perez2, 2005) It is suggested that a negative diagnostic test should not question a clinically typical presentation of CRPS and should not delay treatment. (Birklein, 2005) **B. CRPS-II (previously referred to as causalgia):** Nerve damage may be detected by electrodiagnostic testing, but pain is not contained to that distribution. The diagnosis can also be made where there is evidence of a major nerve lesion. (Stanton-Hicks, 1995) (Harden, 2013) CRPS I and II appear to be clinically similar. (Bruehl, 1999) (Oaklander, 2009) 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. **C. CRPS not otherwise specified (CRPS-NOS):** This diagnosis is not endorsed by ODG. This is a subgroup of patients who do not fully meet the criteria but whose signs and symptoms cannot be explained better by another diagnosis. This subtype was added by the Reflex Sympathetic Dystrophy Syndrome Association to capture any patients previously diagnosed with CRPS who now did not meet criteria. ***Recent research into CRPS subtypes*** Current research suggests there is little evidence for "stages" of CRPS (historically noted as three sequential stages classified as acute, dystrophy and atrophy). Research now points to distinct subtypes. Subtype 1 is a relatively limited syndrome in which vasomotor signs predominate. Subtype 2 is a relatively limited syndrome in which neuropathic pain and/or

	sensory abnormalities predominate. This subtype is thought to be consistent with CRPS II (causalgia) based on electrodiagnostic changes, but EDX is often not sensitive. A third subtype consists of a florid CRPS picture with the greatest predominance of motor/trophic changes with possible osteopenic changes on bone scan. (Harden, 2013) Other authors suggests that subtypes should be made as acute (early) and late (chronic) with a third group labeled as chronic, refractory CRPS. (Zyluk, 2013) *Controversy with establishing the diagnosis:* ***Differential Diagnoses***: It is suggested that in the absence of a differential diagnostic evaluation for patients with a suggested diagnosis of CRPS, management can be abortive and iatrogenic harm may follow. These diagnoses include peripheral neuropathies, infectious processes, inflammatory and vascular disorders, (including dysvascular states in smokers, thrombosis, and arterial insufficiency), and regional musculoskeletal disorders. (Quisel2, 2005) (Stanton-Hicks, 2006) They also include the following conditions: Undetected/unstable fracture; Post-herpetic neuralgia; Motor neuron disease; Diabetic neuropathy; Soft tissue infection; Subclinical nerve entrapments; Atypical nerve compressions; Compartment syndrome; Entrapment neuropathy; Arthritis; Lymphatic or venous obstruction; Raynaud's disease; Rheumatoid arthritis and other rheumatologic disease; Seronegative arthritis; Malignant tumors. (van Eijs, 2011) (Goebel, 2012) (Stanton-Hicks, 2004) A suggested diagnosis of CRPS indicates the urgent need for extensive exploration of the differential diagnosis. (Borchers, 2013) *Immobilization:* Disuse has also been suggested as a differential diagnosis as the clinical signs (including imaging) found can be produced with immobilization. Complications of casting an extremity include joint contractures, compression neuropathy, dystonia, regional osteoporosis, movement-induced pain and swelling. All of these symptoms are similar to findings attributed to CRPS. (Terkelsen, 2008) (Harden, 2013) (Janig, 2004) (Akeson, 1987) (Veldhuizen, 1993) (Okun, 2002) *Immobilization in conjunction with psychological factors:* Disuse in the presence of pre-existing psychopathology is proposed as a link producing a CRPS presentation. Extreme fear of pain can lead to immobilization of the involved extremity. (de Mos, 2009) (Harden, 2013) *The relation of psychiatric and psychological factors and CRPS:* Researchers have suggested that likely differential diagnoses for CRPS should include (1) somatoform disorder, and (2) malingering. Psychiatric overlay has been strongly suggested, particularly in literature dealing with dystonia, and a contribution of functional psychophysiologic links to development of CRPS has not been ruled out. (Bruehl, 2010) (Hawley, 2011) (Verdugo, 2000) (Ochoa, 2010) (Lang, 2010) Theoretical links have been proposed suggesting psychological factors could potentially influence CRPS development but additional prospective tests are required to tests these hypotheses. An actual association between psychosocial factors and CRPS remains controversial, in part due to lack of methodological high-quality studies. (de Mos, 2009) (Beerthuizen, 2009) A recent prospective cohort study revealed no empirical evidence to support a diagnosis of CRPS I patients as psychologically different in a Dutch population using the Symptom Checklist-90. The few prospective studies that are available

	do not point to a unique CRPS I personality or psychosocial pattern. (Marinus, 2011) (Beerthuizen, 2011) (de Mos, 2009) (Bruehl, 2010) *Risk factors:* Financial gain (such as that involved with litigation) has been found to increase the risk of CRPS. (Scarano, 1998) (Goebel, 2012) See also CRPS, treatment; Sympathetically maintained pain (SMP); CRPS, medications; CRPS, prevention; & CRPS, sympathetic blocks (therapeutic)
CRPS, prevention	See CRPS, pathophysiology (clinical presentation & diagnostic criteria).
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, 2002) 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). For average hospital LOS if criteria are met, see Hospital length of stay (LOS).
CRPS, sympathectomy	Not recommended. The practice of surgical, chemical and radiofrequency 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) For average hospital LOS if criteria are met, see Hospital length of stay (LOS).
CRPS, sympathetic blocks (therapeutic)	Recommend local anesthetic sympathetic blocks for limited, select cases, as indicated below. Not recommend IV regional anesthesia blocks. ***Local anesthetic sympathetic blocks:*** Recommended for limited, select cases, primarily for diagnosis of sympathetically mediated pain and therapeutically as an adjunct to facilitate physical therapy/ functional restoration. When used for therapeutic purposes the procedure is not considered a stand-alone

	treatment. The role of sympathetic blocks for treatment of CRPS is largely empirical (with a general lack of evidence-based research for support) but can be clinically important in individual cases in which the procedure ameliorates pain and improves function, allowing for a less painful "window of opportunity" for rehabilitation techniques. (Harden, 2013) Use of sympathetic blocks should be balanced against the side effect ratio and evidence of limited response to treatment. See CRPS, diagnostic tests. ***IV regional anesthesia**:* Not recommended due to lack of evidence for use. This procedure is a technique that allows placement of medications directly in the effected extremity but current literature indicates efficacy is poor. (Harden, 2013) There is no role for IV diagnostic blocks with phentolamine or IVRA with guanethidine. Other procedures include IV regional blocks with lidocaine, lidocaine-methyl-prednisolone, droperidol, ketanserin, atropine, bretylium clonidine, and reserpine. If used, there must be evidence that current CRPS criteria have been met and all other diagnoses have been ruled out. Evidence of sympathetically mediated pain should be provided (see the recommendations below). The reason for the necessity of this procedure over-and-above a standard sympathetic block should also be provided. (Perez, 2010) (Harden, 2013) (Tran, 2010) See also CRPS, treatment. ***General information on sympathetic procedures*** *Current literature:* A recent study indicated that there was low quality literature to support this procedure (some evidence of effect, but conclusions were limited by study design, divergent CRPS diagnostic criteria, differing injection techniques and lack of consistent criteria for positive response). Results were inconsistent and/or extrapolation of questionable reliability with inconclusive evidence to recommend for or against the intervention. (Dworkin, 2013) Other studies have found evidence non-conclusive for this procedure or that low-quality evidence showed this procedure was not effective. (O'Connell, 2013) (Tran, 2010) The blocks are thought to be most beneficial when used early in the disease as an adjunct to rehabilitation with physical or occupational therapy. No controlled trials have shown any significant benefit from sympathetic blockade. (Dworkin 2013) (O'Connell, 2013) (Tran, 2010) (van Eijs, 2012) (Perez, 2010) (van Eijs, 2011) (Nelson, 2006) (Varrassi, 2006) (Cepeda, 2005) (Hartrick, 2004) (Grabow, 2005) (Cepeda, 2002) (Forouzanfar, 2002) (Sharma, 2006) *Historical basis for use:* The use of sympathetic blocks for diagnostic and therapeutic purposes in the management of CRPS is based on a previous hypothesis concerning the involvement of the sympathetic nervous system in the pathophysiological mechanism of the disease. (van Eijs, 2012) It has been determined that a sympathetic mechanism is only present in a small subset of patients, and less than 1/3 of patients with CRPS are likely to respond to sympathetic blockade. See Sympathetically maintained pain (SMP). *Predictors of response:* Researchers have suggested the following are predictors of poor response to blocks: (1) Long duration of symptoms prior to intervention; (2) Elevated anxiety levels; (3) Poor coping skills; (4) Litigation; (5) Allodynia and hypoesthesia. At this time there are no symptoms or signs that predict treatment success. (Hartrick, 2004)

	(Nelson, 2006) (van Eijs, 2012) *Interpretation of block results:* There is a lack of consensus in terms of defining a successful sympathetic block. Based on consensus, a current suggestion of successful block is one that demonstrates an adequate and sustained increase in skin temperature (≥ 1.5° C and/or an increase in temperature to > 34° C) without evidence of thermal or tactile sensory block. A Horner's sign is should be documented for upper extremity blocks. **Recommendations (based on consensus guidelines) for use of sympathetic blocks (diagnostic block recommendations are included here, as well as in CRPS, diagnostic tests):** (1) There should be evidence that all other diagnoses have been ruled out before consideration of use. (2) There should be evidence that the Budapest (Harden) criteria have been evaluated for and fulfilled. (3) If a sympathetic block is utilized for diagnosis, there should be evidence that this block fulfills criteria for success including that skin temperature after the block shows sustained increase (≥ 1.5° C and/or an increase in temperature to > 34° C) without evidence of thermal or tactile sensory block. Documentation of motor and/or sensory block should occur. This is particularly important in the diagnostic phase to avoid overestimation of the sympathetic component of pain. A Horner's sign should be documented for upper extremity blocks. The use of sedation with the block can influence results, and this should be documented if utilized. (Krumova, 2011) (Schurmann, 2001) (4) Therapeutic use of sympathetic blocks is only recommended in cases that have positive response to diagnostic blocks and diagnostic criteria are fulfilled (See #1-3). These blocks are only recommended if there is evidence of lack of response to conservative treatment including pharmacologic therapy and physical rehabilitation. (5) In the initial therapeutic phase, maximum sustained relief is generally obtained after 3 to 6 blocks. These blocks are generally given in fairly quick succession in the first two weeks of treatment with tapering to once a week. Continuing treatment longer than 2 to 3 weeks is unusual. (6) In the therapeutic phase repeat blocks should only be undertaken if there is evidence of increased range of motion, pain and medication use reduction, and increased tolerance of activity and touch (decreased allodynia) is documented to permit participation in physical therapy/ occupational therapy. Sympathetic blocks are not a stand-alone treatment. (7) There should be evidence that physical or occupational therapy is incorporated with the duration of symptom relief of the block during the therapeutic phase. (8) In acute exacerbations of patients who have documented evidence of sympathetically medicated pain (see #1-3), 1 to 3 blocks may be required for treatment. (9) A formal test of the therapeutic blocks should be documented (preferably using skin temperature). (Burton, 2006) (Stanton-Hicks, 2004) (Stanton-Hicks, 2006) (International Research Foundation for RSD/CRPS, 2003) (Colorado, 2006) (Washington, 2002) (Rho, 2002) (Perez, 2010) (van Eijs, 2011)

CRPS, treatment	Recommend hierarchy of options as indicated below. The goal is to improve function. There are no evidence-based treatment guidelines, but several groups have begun to organize treatment algorithms that are consensus based. There is currently no intervention for CRPS that can be considered to be supported by strong evidence of efficacy. (Ribbers, 2003) (Stanton-Hicks, 2006) (O'Connell, 2013) *Interdisciplinary management* is recommended emphasizing functional restoration. (Harden, 2013) (Singh, 2004) (Albazaz, 2008) (Hsu, 2009) **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 may temporarily increase symptoms, particularly if too aggressive. (b) *Next steps*: Increase flexibility with introduction of gentle active ROM and stretching (to treat accompanying myofascial pain syndrome). Other interventions to enhance participation in rehabilitation 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, and posture and modifications at home and work. **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, after 6 to 8 weeks, identification of stressors, and identification of comorbid Axis I psychiatric disorders (depression, anxiety, panic and post-traumatic stress). **3. *Pain management:*** *Pharmacological treatment:* See CRPS, medications. *Invasive treatment:* The role of sympathetic blocks is largely empirical with lack of solid evidence. See CRPS, sympathetic blocks, (therapeutic) for more specific information and criteria for use of sympathetic treatment. *Local anesthetic sympathetic blocks:* Recommended for limited, select cases, primarily for diagnosis of sympathetically mediated pain and therapeutically as an adjunct to facilitate physical therapy/ functional restoration. When used for the latter the procedure is not considered a stand-alone procedure. The role of sympathetic blocks for treatment of CRPS is largely empirical (with a general lack of evidence-based research for support) but can be clinically important in individual cases in which the procedure ameliorates pain and improves function, allowing for a less painful "window of opportunity" for rehabilitation techniques. (Harden, 2013) *Sympathectomy:* Not recommended. See CRPS, sympathectomy. *IV regional anesthesia:* Not recommended due to lack of evidence for use. See CRPS, sympathetic blocks, (therapeutic); Intravenous regional

	sympathetic blocks (for RSD/CRPS). *Epidural infusions for sympathetic blockade:* Not recommended due to lack of evidence for use and high risk of complications including infection. There is one randomized controlled trial that reported improvement. A study that included both randomized and open label design (26 patients) using clonidine showed pain relief, but the authors considered this experimental and the study has not been repeated. Infections occurred in 6/19 patients who ultimately received the treatment. (Rauck, 1993) *Brachial plexus blocks:* Not recommended due to the lack of evidence for use and risk of complications including infection, intravascular injection, pneumothorax, and phrenic nerve paralysis. (Harden, 2013) (Tran, 2010) *Intrathecal drugs: Opioids* are not recommended. *Baclofen* may play a limited, end-stage role for treatment for patients with dystonia, the area which the limited research addresses. The first study was conducted in 7 patients using IASP criteria. Six of these received a pump. Greater effect was found in the arms than legs. When followed for a year, the largest improvement was noted in the first three months with stabilization around a one year period. Lack of responsiveness to intrathecal baclofen declined in 30% of patients once delivery was switched from external to implantable treatment. A large number of adverse events were noted with the most common being post-dural headache. In this second study the authors indicated that to enhance therapeutic potential, methods to improve patient selection and catheter-pump integrity were warranted. Increasing the infusion rate did not result in improvement of dystonia. The authors also note that significant improvement in global intense pain, sharp pain, dull pain and deep pain occurred in the first six months of this open design, but after this period the scores leveled despite further improvement of dystonia and continued ITB dose escalation. (van der Plas, 2013) (van Rijn, 2009) *Spinal Cord Stimulator:* See CRPS, spinal cord stimulators. See also CRPS, pathophysiology (clinical presentation & diagnostic criteria); CRPS, medications; CRPS, sympathetic blocks (therapeutic); Intravenous regional sympathetic blocks (for RSD/CRPS); & Sympathetically maintained pain (SMP).
Current perception threshold (CPT) testing	Not recommended. Current perception threshold testing is considered experimental or investigational, as there is inadequate scientific literature to support any conclusions regarding the effects of this testing on health outcomes..
Cyclobenzaprine (Flexeril®)	Recommended as an option, using a short course of therapy. 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; this medication is not recommended for longer than 2-3 weeks. 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 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. See also Muscle relaxants (for pain), Cyclobenzaprine listing.
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®).
Cytochrome p450 testing	See Cytokine DNA testing.
Cytokine DNA testing	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. 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) In a research setting, plasma levels of various cytokines may give information on the presence, or even predictive value of inflammatory processes involved in autoimmune diseases such as rheumatoid arthritis. (Kokkonen, 2010) See also Genetic testing for potential opioid abuse.
Darvon® (propoxyphene)	See Propoxyphene (Darvon®).
Demerol® (meperidine)	See Meperidine (Demerol®).
Deplin® (L-methylfolate)	Not recommended. Deplin® (L-methylfolate) is a prescription medical food, for the dietary management of suboptimal folate, a naturally occurring B vitamin, in depressed patients. L-methylfolate is not an antidepressant, but may make antidepressants work better by correcting folate levels in the brain See also Vitamin B & Medical foods.
Detoxification	Most commonly recommended when there is evidence of substance misuse or abuse, evidence that medication is not efficacious, or evidence of excessive complications related to use. See MTUS Opioids Treatment Guidelines (substance disorders, tolerance, dependence, addiction) for definitions. Detoxification is defined as a medical intervention that manages a patient through withdrawal syndromes. While the main indication as related to substance-related disorders is evidence of aberrant

	drug behaviors, other indications for detoxification have been suggested. These include the following: (1) Intolerable side effects; (2) Lack of response to current pain medication treatment (particularly when there is evidence of increasingly escalating doses of substances known for dependence); (3) Evidence of hyperalgesia; (4) Lack of functional improvement; and/or (5) Refractory comorbid psychiatric illness. It can therefore be seen that a recommendation for detoxification does not necessarily imply a diagnosis of addiction, or of substance-related disorder. There are no specific guidelines that have been developed for detoxification for patients with chronic pain. This intervention does not constitute complete substance abuse treatment. The process of detoxification includes evaluation, stabilization, and preparation of the patient for further treatment that should be specifically tailored to each patient's diagnostic needs. Complete withdrawal of all medications is not always recommended, although evidence of abuse and/or dependence strengthens the rationale for such.(TIP 45, 2006) (Wright, 2009) (Benzon, 2005) See MTUS Opioids Treatment Guidelines (substance disorders, tolerance, dependence, addiction) for definitions. For average hospital LOS if criteria are met, see Hospital length of stay (LOS).
Diabetic neuropathy	Recommend screening for diabetic neuropathy. With the increased prevalence of diabetes in the US, there has also been an increase in the presentation of diabetic neuropathy (DN) with approximately two-thirds of diabetic patients having minimal to full-blown symptoms. (Bansal, 2006) This is a condition that can confound the presentation of chronic pain from work-related injuries. The American Academy of Neurology suggests that the diagnosis of DN should be considered in patients with somatic or autonomic neuropathy and when other causes of neuropathy have been excluded. (ADA/ANA, 1988) Approximately 10% to 20% of diabetic patients have "other causes" of neuropathy. At least two out of the five following criteria are needed for diagnosis: 1) symptoms; 2) signs; 3) electrodiagnostic tests; 4) quantitative sensory; & 5) autonomic testing. Presentations and issues are outlined below: Distal Symmetrical Polyneuropathy: The most common presentation of DN - 75%. (Bansal, 2006) This is a stocking and glove presentation to the knee, and with a latter presentation in the fingers. There are two variants: 1) Large Fiber Disease: presents with painless paresthesias, and impairment of vibration, joint position, sensation and pressure, and loss of ankle reflex. EMG shows slowing of nerve conduction; 2) Small fiber disease: results in pain and burning. Persistent Painful Neuropathy: About 10%. (Bansal, 2006) This pain is usually worse at night, and is described as burning, pins and needles, shooting, aching, jabbing, sharp, cramping, tingling, cold and allodynia. This condition can occur prior to the onset of clinically diagnosed diabetes. Opioid tolerance and addiction has been found in this class of patients. This pain may decrease with hyperglycemia control. Proximal Diabetic Neuropathy (also referred to as Diabetic Amyotrophy, or

	Diabetic Lumbosacral Radiculoplexus Neuropathy, or Diabetic Polyradiculopathy): (Bansal, 2006) Symptoms are consistent with proximal nerve involvement and include pain in the low back, hip and/or anterior thigh, which can be unilateral or bilateral. Thoracic radiculopathy may be involved as well as upper limb involvement (the latter mostly being mononeuropathies). The onset may be abrupt or chronic. Weight loss is also common. Pain and weakness is frequently persistent. This condition can coexist with distal symmetrical polyneuropathy. EMG/NCV shows reductions in the compound muscles and SNAPs with mild slowing of the NCVs. EMGs also show frequent fibrillation potentials (including lumbosacrals). This condition is considered under recognized and has been confused with radiculopathy secondary to disc disease. (Dyck, 2001) Limb Neuropathy: Secondary to nerve infarction. (Bansal, 2006) When associated with nerve infarction, there is an acute onset, with eventual weakness and atrophy. The most common nerves are median, ulnar and peroneal. (Wiffen-*Cochrane*, 2005) Entrapment: more common. Electrodiagnostic testing shows segmental nerve conduction slowing. A common presentation is carpal tunnel syndrome (3 times more common in diabetics). (Bansal, 2006) Other frequent presentations include the ulnar, radial, lateral femoral cutaneous, peroneal, medial and lateral plantar nerves. Nerve conduction studies in DN: 1) Large Fiber Neuropathies: Motor nerve conduction is affected but is often insensitive. The diagnosis is generally made by excluding other causes of neuropathy. Entrapment is common and usually shows unilateral NCV changes. Overall, even in subclinical states, NCV is gradually diminished, and there can be evidence of decreased amplitude of evoked muscles or nerve action potentials (decreased sensory and motor amplitudes). (Bansal, 2006) 2) Small Fiber Neuropathies: Small fiber function is not detectable using standard electrophysiologic measures. Treatment: The number needed to treat for different drugs for 50% pain relief include: 1) tricyclic antidepressants, 1.4; 2) dextromethorphan, 1.9; 3) carbamazepine 3.3; 4) Tramadol 3.4; 5) gabapentin, 4.3 (Wiffen-*Cochrane*, 2005) (increased from 3.7 in the latest Cochrane review); 6) capsaicin 5.9; 7) SSRIs, 6.7. (Sindrup, 1999) It is advised to avoid opioids due to possible addiction. The FDA has approved the use of pregabalin (Lyrica®) for the treatment of DM. See also Duloxetine (Cymbalta®).
Diagnostic criteria for CRPS	See CRPS, diagnostic criteria.
Diazepam (Valium)	Not recommended. See Benzodiazepines.
Diclofenac	Not recommended as first line due to increased risk profile. A large systematic review of available evidence on NSAIDs confirms that diclofenac, a widely used NSAID, poses an equivalent risk of cardiovascular events to patients as did rofecoxib (Vioxx), which was taken off the market. According to the authors, this is a significant issue and doctors should avoid diclofenac because it increases the risk by about 40%. For a patient who has a 5% to 10% risk of having a heart attack, that is a significant increase in absolute risk, particularly if there are other drugs that don't seem to have that risk. For people at very low risk, it may be an

	option. (McGettigan, 2011) Another meta-analysis supported the substantially increased risk of stroke with diclofenac, further suggesting it not be a first-line NSAID. (Varas-Lorenzo, 2011) In this nationwide cohort study the traditional NSAID diclofenac was associated with the highest increased risk of death or recurrent myocardial infarction (hazard ratio, 3.26; 95% confidence interval, 2.57 to 3.86 for death/MI at day 1 to 7 of treatment) in patients with prior MI, an even higher cardiovascular risk than the selective COX-2 inhibitor rofecoxib, which was withdrawn from the market due to its unfavorable cardiovascular risk profile. (Schjerning, 2011) According to FDA MedWatch, postmarketing surveillance of topical diclofenac has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation. If using diclofenac then consider discontinuing as it should only be used for the shortest duration possible in the lowest effective dose due to reported serious adverse events. Post marketing surveillance has revealed that treatment with all oral and topical diclofenac products may increase liver dysfunction, and use has resulted in liver failure and death. Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac. (FDA, 2011) In 2009 the FDA issued warnings about the potential for elevation in liver function tests during treatment with all products containing diclofenac sodium. (FDA, 2009) With the lack of data to support superiority of diclofenac over other NSAIDs and the possible increased hepatic and cardiovascular risk associated with its use, alternative analgesics and/or nonpharmacological therapy should be considered. The AGS updated Beers criteria for inappropriate medication use includes diclofenac. (AGS, 2012) Diclofenac is associated with a significantly increased risk of cardiovascular complications and should be removed from essential-medicines lists, according to a new review. The increased risk with diclofenac was similar to Vioxx, a drug withdrawn from worldwide markets because of cardiovascular toxicity. Rofecoxib, etoricoxib, and diclofenac were the three agents that were consistently associated with a significantly increased risk when compared with nonuse. With diclofenac even in small doses it increases the risk of cardiovascular events. They recommended naproxen as the NSAID of choice. (McGettigan, 2013) See also NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines. See also Zorvolex (diclofenac).
Diclofenac potassium (Cataflam®)	Not recommend diclofenac as first line due to increased risk profile. See Diclofenac listing. See also NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Diclofenac Potassium (Cataflam®) listing for more information and references.
Diclofenac sodium (Voltaren®,	Not recommend diclofenac as first line due to increased risk profile. See Diclofenac listing. See also NSAIDs (non-steroidal anti-inflammatory

Voltaren-XR®)	drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Diclofenac Sodium (Voltaren®, Voltaren-XR®) listing for more information and references, where the oral form had been recommended with cautions. See also Topical analgesics, where Voltaren Gel is recommended for osteoarthritis after failure of an oral NSAID, or contraindications to oral NSAIDs, or for patients who cannot swallow solid oral dosage forms.
Diclofenac, topical (Flector®, Pennsaid®, Voltaren® Gel)	Not recommended as a first-line treatment, but recommended as an option for patients at risk of adverse effects from oral NSAIDs, after considering the increased risk profile with diclofenac. See specific topical diclofenac listings: Flector® patch (diclofenac epolamine); Pennsaid® (diclofenac sodium topical solution); & Voltaren® Gel (diclofenac). For more details, see also Topical analgesics, Non-steroidal antinflammatory agents (NSAIDs), and the diclofenac topical listing.
Diflunisal (Dolobid®)	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Diflunisal (Dolobid®) listing for more information and references.
DMSO (dimethylsulfoxide)	See 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 (Marinol)	Dronabinol is a synthetic THC (tetrahydrocannabinol). See Cannabinoids.
Drug testing	See MTUS Opioids Treatment Guidelines for recommendations on urine drug testing.
Drug therapy	See Medications.
Dry needling	The term dry needling, using solid needles for therapy, without an injectable liquid, is used in the context of acupuncture, trigger point injections, or percutaneous needle tenotomy. See Acupuncture or Trigger point injections (TPIs) in this Chronic Pain guidelines or MTUS Acupuncture Medical Treatment guidelines.
Duexis® (ibuprofen & famotidine)	Not recommended as a first-line drug. Horizon Pharma recently announced the launch of Duexis, a combination of ibuprofen 800 mg and famotidine 26.6 mg, indicated for rheumatoid arthritis and osteoarthritis. (FDA, 2012) Ibuprofen (eg, Motrin, Advil) and famotidine (eg, Pepcid) are also available in multiple strengths OTC, and other strategies are recommended to prevent stomach ulcers in patients taking NSAIDS. See NSAIDs, GI symptoms & cardiovascular risk, where Proton pump inhibitors (PPIs) are recommended. With less benefit and higher cost, using Duexis as a first-line therapy is not justified.
Duloxetine	Recommended as an option in first-line treatment of neuropathic pain.

(Cymbalta®)	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 (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 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) An FDA panel broadened the indication to include the treatment of chronic pain. (FDA, 2010) Regulatory approval followed a positive vote regarding the use of duloxetine to treat chronic low back pain, but the committee did not express the same confidence in the drug's usefulness as a treatment for osteoarthritis. Despite this, duloxetine has been approved for both chronic low back pain and osteoarthritis. The recommended dose is 60 mg daily. Duloxetine delayed-release capsules previously were approved for the treatment of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, and fibromyalgia. (FDA2, 2010) See MTUS Low Back Complaints.
Duragesic® (fentanyl transdermal system)	See MTUS Opioids Treatment Guidelines. 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. Due to the significant side effects, not for use in routine musculoskeletal pain. The FDA will require color changes to the writing that appears on fentanyl pain patches (Duragesic and generics) so they can be seen more easily and to emphasize that unintended exposure can cause death. (FDA, 2013) This is part of an effort to prevent accidental exposure to the patches, which can cause serious harm and death in children, pets, and others. (FDA, 2013) See Fentanyl.
Dynatron STS	See Sympathetic therapy.
Dysport	See Botulinum toxin.
Ear-acupuncture	See Auricular electroacupuncture.
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 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, offers 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) An RCT with 1,077 patients using education and guidelines-based clinical management compared to standard primary care management, found that the program improved short- and long-term work disability outcomes and was cost-effective. Fewer patients received long-term disability compensation in the intervention group than in the control group, and lost-work episodes were shorter in the intervention group than in the control group. Each dollar invested generated a benefit of 11 dollars. (Abásolo, 2005)
Edluar (zolpidem tartrate)	In late 2009 the FDA approved Edluar (zolpidem tartrate) sublingual tablets, 5 and 10 mg for the treatment of insomnia. This new formulation of the zolpidem (Ambien) tablets does not appear to have any therapeutic benefit over existing generic zolpidem. (FDA, 2010) See Zolpidem (Ambien®).
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 more specific therapy. The following are choices: Galvanic stimulation, H-wave stimulation (devices), Interferential current stimulation (ICS), Microcurrent electrical stimulation (MENS devices), Neuroreflexotherapy, Neuromuscular electrical stimulation (NMES), Percutaneous electrical nerve stimulation (PENS), Percutaneous neuromodulation therapy (PNT), Spinal cord stimulation, Sympathetic therapy, Electroceutical therapy (bioelectric nerve block), Transcutaneous electrical neurostimulation (TENS); & Scrambler therapy (Calmare®).
Electroceutical therapy (bioelectric nerve block)	Not recommended. Electroceutical therapy (also known as bioelectric nerve block) is experimental and investigational for the treatment of acute pain or 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)
Electrodiagnostic testing (EMG/NCS)	Recommended needle EMG or NCS, depending on indications. Surface EMG is not recommended. Electromyography (EMG) and Nerve Conduction Studies (NCS) are generally accepted, well-established and widely used for localizing the source of the neurological symptoms and establishing the diagnosis of focal nerve entrapments, such as carpal tunnel syndrome or radiculopathy, which may contribute to or coexist with CRPS II (causalgia), when testing is performed by appropriately trained neurologists or physical medicine and rehabilitation physicians (improperly performed testing by other providers often gives inconclusive results). As CRPS II occurs after partial injury to a nerve, the diagnosis of the initial nerve injury can be made by electrodiagnostic studies. The later development of sympathetically mediated symptomatology however, has no pathognomonic pattern of abnormality on EMG/NCS. (Colorado, 2002) EMG and NCS are separate studies and should not necessarily be done together. NCS is recommended in patients with clinical signs of CTS who may be candidates for surgery, but EMG is not generally necessary. NCS is not recommended, but EMG is recommended as an option (needle, not surface) to obtain unequivocal evidence of radiculopathy, after 1-month conservative therapy, but EMG's are not necessary if radiculopathy is already clinically obvious. Electrodiagnostic studies should be performed by appropriately trained Physical Medicine and Rehabilitation or Neurology physicians. See also Monofilament testing. For more information see MTUS Forearm, Wrist, and Hand Complaints, MTUS Low Back Complaints, and MTUS Neck and Upper Back Complaints. Below are the Minimum Standards from that chapter. **Minimum Standards for electrodiagnostic studies:** The American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) recommends the following minimum standards: (1) EDX testing should be medically indicated. (2) Testing should be performed using EDX equipment that provides assessment of all parameters of the recorded signals. Studies performed with devices designed only for “screening purposes” rather than diagnosis are not acceptable.

	(3) The number of tests performed should be the minimum needed to establish an accurate diagnosis. (4) NCSs (Nerve conduction studies) should be either (a) performed directly by a physician or (b) performed by a trained individual under the direct supervision of a physician. Direct supervision means that the physician is in close physical proximity to the EDX laboratory while testing is underway, is immediately available to provide the trained individual with assistance and direction, and is responsible for selecting the appropriate NCSs to be performed. (5) EMGs (Electromyography - needle not surface) must be performed by a physician specially trained in electrodiagnostic medicine, as these tests are simultaneously performed and interpreted. (6) It is appropriate for only 1 attending physician to perform or supervise all of the components of the electrodiagnostic testing (e.g., history taking, physical evaluation, supervision and/or performance of the electrodiagnostic test, and interpretation) for a given patient and for all the testing to occur on the same date of service. The reporting of NCS and EMG study results should be integrated into a unifying diagnostic impression. (7) In contrast, dissociation of NCS and EMG results into separate reports is inappropriate unless specifically explained by the physician. Performance and/or interpretation of NCSs separately from that of the needle EMG component of the test should clearly be the exception (e.g. when testing an acute nerve injury) rather than an established practice pattern for a given practitioner. (AANEM, 2009)
Embeda® (morphine /naltrexone)	See MTUS Opioids Treatment Guidelines.This medication is designed to alter oral use and thus prevent patients from abusing opioids. As it is resistant to being crushed or dissolved, Embeda does not allow for nasal use (insufflation), chewing and /or intravenous use. Other tamper-resistant agents on the market include Suboxone (buprenorphine/ naloxone), Opana (oxymorphone), Exalgo (hydromorphone), and OxyContin (oxycodone controlled release). The FDA has approved morphine sulfate and naltrexone hydrochloride extended-release capsules (Embeda) for once- or twice-daily use in the management of moderate to severe pain when continuous, around-the-clock opioid analgesic therapy is warranted for an extended period. The capsules contain morphine pellets with a sequestered inner core of the opioid antagonist naltrexone that is released when the product is crushed or chewed, thereby discouraging tampering and drug abuse. Approval of the product was based on data from 12 clinical studies, including a phase 3 study showing that its use provided significant pain relief compared with placebo in patients with severe pain caused by osteoarthritis of the hip or knee. (FDA, 2009) In this RCT pain relief was statistically significantly superior for those treated with Embeda compared to the control group (Trevino, 2009) The FDA's latest list of drugs to monitor after having identified potential signs of serious risks or new safety information includes Embeda for withdrawal symptoms not associated with misuse. (FDA, 2011) *Black Box Warning:* Embeda is not intended for PRN use. Embeda can be abused in a manner similar to other

	opioid agonists. It is only recommended for opioid tolerant patients. Patients on this drug should not ingest alcohol, including that included in prescription and non-prescription medications. Fatal respiratory depression can occur with use.
Epidiolex™ (cannabidiol)	Epidiolex is an oral liquid that contains plant-derived cannabidiol without THC for use in the treatment of intractable epilepsy. See Cannabinoids.
Epidural steroid injections (ESIs)	See MTUS Low Back Complaints for recommendations.
Escitalopram (Lexapro®)	See Anxiety medications in chronic pain, Escitalopram (Lexapro®) listing, and Antidepressants for chronic pain, SSRIs
Estazolam	Not recommended. See Benzodiazepines.
Eszopicolone (Lunesta)	Not recommended for long-term use, but recommended for short-term use.
Etodolac (Lodine®, Lodine XL®)	See NSAIDS(non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Etodolac (Lodine®, Lodine XL®) listing for more information and references. A large systematic review of available evidence on NSAIDs confirms that naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk. Etodolac in the unpaired analyses had a risk profile similar to that of rofecoxib, but the pair-wise analyses are likely to be less confounded, and these analyses showed etodolac to be similar to two low risk drugs, ibuprofen and naproxen. (McGettigan, 2011)
Evzio® (naloxone)	Not recommended except on a case-by-case basis after preauthorization, as naloxone is not generally recommended in ODG for outpatient, pre-hospital use by untrained lay users. See Naloxone (Narcan®). Evzio® is an FDA-approved naloxone drug-device combination indicated for the emergency treatment of opioid overdose. The device is designed to guide an untrained lay user through the process of use for overdose reversal. It is labeled for prehospital lay use. It does not require pre use training nor does it require assembly (as required for existing intramuscular or off-label intranasal use). (Beletsky, 2015) See Naloxone (Narcan®) for complete information.
Exalgo (hydromorphone)	Exalgo (hydromorphone) is a once-a-day extended release opioid formulation for the management of moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time, with an FDA black box warning.
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 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. (Burleson, 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) A meta-analysis concluded that there is gold level evidence that supervised aerobic exercise training has beneficial effects on physical capacity and fibromyalgia syndrome (FMS) symptoms, and strength training may also have benefits on some FMS symptoms. (Busch-*Cochrane*, 2007)
Facet blocks	Recommend no more than one therapeutic intra-articular lumbar block when facet joint pain is suspected, but not cervical blocks. Recommend no more than one set of medial branch diagnostic blocks prior to facet neurotomy, but not recommend medial branch blocks except as a diagnostic tool. Not recommend a multiple series of facet joint injections. Not recommend thoracic facet joint injections. Refer to the MTUS Low Back Complaints and Neck and Upper Back Complaints for detailed information.
Fenoprofen (Nalfon®)	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Fenoprofen (Nalfon®) listing for more information and references.
Fentanyl	See MTUS Opioids Treatment Guidelines for recommendations on the use of opioids such as 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. The FDA has approved an immediate-release transmucosal tablet formulation of fentanyl (Abstral; ProStraken, Inc) for the management of breakthrough cancer pain. Because Abstral is subject to abuse and misuse, the product was approved with a risk evaluation and mitigation strategy (REMS) that includes a restricted distribution program requiring registration of prescribers, pharmacies, and patients. (FDA, 2011)
Fentora® (fentanyl effervescent buccal tablet)	See MTUS Opioids Treatment Guidelines for recommendations on the use of opioids.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.
Fibromyalgia syndrome (FMS)	Overview of this pain syndrome (not a procedure): Despite the chronicity and complexity of fibromyalgia syndrome (FMS), there are pharmacological and nonpharmacological interventions available that have clinical benefit. Based on current evidence, a stepwise program emphasizing education, certain medications, exercise, cognitive therapy, or all 4 should be recommended. Current evidence suggests efficacy of low-dose tricyclic antidepressants, cardiovascular exercise, cognitive behavioral therapy, and patient education. A number of other commonly used FMS therapies, such as trigger point injections, have not been adequately evaluated. (Goldenberg-JAMA, 2004) Definitions: Criteria for the classification of Fibromyalgia: (1) History of widespread pain. (2) Pain in 11 of 18 tender point sites on digital palpation. For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia, but fibromyalgia is a controversial & self-perpetuating diagnosis - screen for related conditions & return to regular activities as soon as possible. (Wolfe, 1990) Although the American College of Rheumatology (ACR) criteria for fibromyalgia are used to identify individuals with both widespread pain and tenderness, individuals who meet these criteria are not a homogeneous group. There are three distinct subgroups of patients with fibromyalgia. There appears to be a group of fibromyalgia patients who exhibit extreme tenderness but lack any associated psychological/cognitive factors, an intermediate group who display moderate tenderness and have normal mood, and a group in whom mood and cognitive factors may be significantly influencing the symptom report. (Giesecke, 2003) For fibromyalgia, there is limited evidence of the effectiveness of amitriptyline. (Moulin, 2001) In treating pain associated with fibromyalgia, gabapentin-treated patients displayed a significantly greater improvement in their average pain severity score. (Arnold, 2007) In June 2007 FDA announced the approval of pregabalin (Lyrica®) as the first approved treatment for fibromyalgia. Two double-blind, controlled clinical trials, involving about 1,800 patients, supported approval for use in treating fibromyalgia with doses of 300 milligrams or 450 milligrams per day. (FDA, 2007) Progressive walking, simple strength training, and stretching improved functional status, key symptoms, and self-efficacy in women with fibromyalgia actively treated with medication, according to the results of a randomized controlled trial reported in the November 12 issue of the *Archives of Internal Medicine*. The benefits of exercise are enhanced when combined with targeted self-management education. (Rooks, 2007) On June 13, 2008, the FDA approved a new indication for duloxetine HCl delayed-release capsules (Cymbalta®; Eli Lilly and Company), allowing their use for the management of fibromyalgia in adults. Previously, only pregabalin (Lyrica®; Pfizer, Inc) was approved to treat this painful condition. 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) This meta-analysis concluded that there is gold level evidence that supervised aerobic exercise training has beneficial effects on physical capacity and fibromyalgia syndrome (FMS) symptoms, and strength training may also have benefits on some FMS symptoms. (Busch-*Cochrane*, 2007) Obesity is linked to an increased risk for fibromyalgia. Women who reported exercising 4 times per week had a 29% lower risk of FM [fibromyalgia] compared with inactive women. Women who reported the highest exercise level had a relative risk (RR) of 0.77 for the development of fibromyalgia, and there was a weak dose-response association between level of physical exercise and the risk for fibromyalgia. Compared with normal-weight women, overweight or obese women had a 60% to 70% higher risk for fibromyalgia. BMI was an independent risk factor for fibromyalgia. Compared with normal-weight women who exercised at least 1 hour per week, overweight or obese women with a similar activity level had a 72% higher risk for fibromyalgia, whereas overweight or obese women who exercised less than 1 hour per week or who were inactive had more than double the risk for fibromyalgia. (Mork, 2010) Tai chi may be a helpful intervention for patients with fibromyalgia. (Wang, 2010) Women with fibromyalgia can reduce symptoms of the disease and improve their function by practicing the mind-body techniques of yoga, a new RCT concludes. The results suggested that yoga led to a beneficial shift in how patients cope with pain, including greater use of adaptive pain-coping strategies, such as engaging in activities despite pain, acceptance of their condition, the use of religion as a coping mechanism, and the ability to relax. (Carson, 2010) In the latest American College of Rheumatology diagnostic criteria for fibromyalgia, the most important diagnostic variables were a widespread pain index (a measure of the number of painful body regions) and categorical scales for cognitive symptoms, unrefreshed sleep, fatigue, and number of somatic symptoms. (Wolfe, 2010) A program aimed at easing stress with meditation and yoga may not be much help for patients with fibromyalgia, a recent RCT suggests. (Schmidt, 2011) Vagus nerve stimulation may show early promise in fibromyalgia. The study included 14 adult women who had physician-diagnosed fibromyalgia for at least 2 years and were refractory to conventional pharmacological treatment (i.e., nonsteroidal anti-inflammatories, tricyclic antidepressants, and anticonvulsants). They were surgically implanted with a vagus nerve stimulation (VNS) device. The results may represent a placebo effect related to being in a treatment trial necessitating surgery, feeling a sensory stimulus throughout the day and having high hopes for a good therapeutic outcome. (Lange, 2011) Low doses of the muscle relaxant cyclobenzaprine, taken at bedtime, may help people with fibromyalgia sleep better and feel less pain, according to a small study. Pain declined 26% in the drug group over the study, only 18% more than in the placebo group. (Lederman, 2011) In this study trazodone significantly improved fibromyalgia severity and associated symptomatology. Its combination with pregabalin potentiated this improvement and the tolerability of the drugs in

	association was good. (Calandre, 2011)
Fioricet	Not recommended. See Barbiturate-containing analgesic agents (BCAs).
Flavocoxid (Limbrel)	Not recommended for treatment of chronic pain. See Limbrel (flavocoxid / arachidonic acid).
Flector® patch (diclofenac epolamine)	Not recommended as a first-line treatment. See the Diclofenac listing, where topical diclofenac is recommended for osteoarthritis after failure of an oral NSAID or contraindications to oral NSAIDs, after considering the increased risk profile with diclofenac, including topical formulations. Flector patch is FDA indicated for acute strains, sprains, and contusions. (FDA, 2007) On 12/07/09 the FDA issued warnings about the potential for elevation in liver function tests during treatment with all products containing diclofenac. Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac. (FDA, 2009) The efficacy in clinical trials for topical NSAIDs 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. These medications may be useful for chronic musculoskeletal pain, but there are no long-term studies of their effectiveness or safety. In addition, there is no data that substantiate Flector efficacy beyond two weeks. See also Topical analgesics, Non-steroidal antinflammatory agents (NSAIDs), and the diclofenac topical listing.
Flexeril® (Cyclobenzaprine)	See Cyclobenzaprine (Flexeril®).
Fluoxetine	See SSRIs (selective serotonin reuptake inhibitors).
Flurazepam	Not recommended. See Benzodiazepines.
Flurbiprofen (Ansaid®)	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Flurbiprofen (Ansaid®) listing for more information and references. For topical use, see Topical analgesics, Non-steroidal antinflammatory agents (NSAIDs).
Fluvoxamine	See SSRIs (selective serotonin reuptake inhibitors).
FMRI (functional magnetic resonance imaging)	See Functional imaging of brain responses to pain; & Functional MRI.
Functional imaging of brain responses to pain	Not recommended except in research settings. 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. 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) In this study functional magnetic resonance imaging (fMRI) combined with support vector machine (SVM) algorithms accurately predicted thermal pain 81% of the time in healthy subjects. (Brown, 2011) There is a distinct neurologic pattern on functional MRI (fMRI) that is specific to heat-induced pain and sensitive to the analgesic effects of opioids. This nociceptive pain signature could be used to confirm pain in those who cannot report accurately (eg, the very old, very young, cognitively impaired) or whose reports are not completely trusted by medical or legal decision-makers, but it should not be used as a pain lie detector because some individuals may have real pain that is not captured by this pattern. The authors conclude that more study is needed. (Wager, 2013)
Functional improvement measures	Recommended. See MTUS Opioids Treatment Guidelines (Clinically Meaningful Improvement in Pain and Function). 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)
Functional MRI	Not recommended. May be appropriate in a research setting. 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) In this study functional magnetic

	resonance imaging (fMRI) combined with support vector machine (SVM) algorithms accurately predicted thermal pain 81% of the time in healthy subjects. (Brown, 2011) The algorithms are based on mind reading technology that has been used in cognitive neuroscience, but the technology is not yet ready for clinical application. Researchers are investigating whether this is an objective biomarker for chronic pain that could not only eventually help monitor pain therapies but also distinguish patients with real chronic pain. (Ung, 2012)
Functional restoration programs (FRPs)	Recommended for selected patients with chronic disabling pain, 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) 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. See also MTUS Low Back Complaints.
GABAdone™	Not recommended. GABAdone™ is a medical food that is a proprietary blend of Choline Bitartrate, Glutamic Acid, 5-Hydroxytryptophan, and GABA. See Medical foods.
Gabapentin (Neurontin®)	Recommended for some neuropathic pain conditions and fibromyalgia. (Wiffen-*Cochrane*, 2013) 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	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)

Genetic testing for potential opioid abuse	While there appears to be a strong genetic component to addictive behavior, current research is experimental in terms of testing for this. Studies are inconsistent, with inadequate statistics and large phenotype range. Different studies use different criteria for definition of controls. More work is needed to verify the role of variants suggested to be associated with addiction and for clearer understanding of their role in different populations. (Levran, 2012) Translating pharmacogenetics to clinical practice has been particularly challenging in the context of pain, due to the complexity of this multifaceted phenotype and the overall subjective nature of pain perception and response to analgesia. Overall, numerous genes involved with the pharmacokinetics and dynamics of opioids response are candidate genes in the context of opioid analgesia. Overall, the level of evidence linking genetic variability to opioid response is strong; however, there has been no randomized clinical trial on the benefits of genetic testing prior to oxycodone therapy. On the other hand, predicting the analgesic response to morphine based on pharmacogenetic testing is more complex; though there was hope that simple genetic testing would allow tailoring morphine doses to provide optimal analgesia, this is unlikely to occur. A variety of polymorphisms clearly influence pain perception and behavior in response to pain. However, the response to analgesics also differs depending on the pain modality and the potential for repeated noxious stimuli, the opioid prescribed, and even its route of administration. (Vuilleumier, 2012) See also Cytokine DNA testing.
Glucosamine (and Chondroitin sulfate)	Recommended as an option (glucosamine sulfate only) 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). For all herbals and dietary supplements, there may be concerns for potential interactions with prescription and over-the-counter medications and lack of manufacturing quality controls. (Richy, 2003) (Ruane, 2002) (Towheed-Cochrane, 2001) (Braham, 2003) (Reginster, 2007) (Reginster, 2001) (Pavelka, 2002) (Clegg, 2006) (Reichenbach, 2007) 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, but the GAIT investigators did not use glucosamine sulfate (GS). (Distler, 2006) 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.] See also MTUS Knee Complaints, since many studies involved arthritis of the knee. *Recent research:* The benefit of glucosamine with or without chondroitin remains unclear. (Sawitzke, 2008) However, the possible interaction between chondroitin and anticoagulants may be an issue for some patients. (Rozenfeld, 2004) Glucosamine and/or chondroitin may not be helpful for patients with osteoarthritis of the hip or knee, according to the results of a recent meta-analysis in *BMJ*, but the authors concluded that neither of the preparations are dangerous, and there is no harm in having patients continue these preparations as long as they perceive a benefit and cover the costs of treatment themselves. (Wandel, 2010)
Gralise (gabapentin enacarbil ER)	Not recommended. See MTUS Knee Complaints.
Haveos™ genetics opioid abuse testing	The Haveos genetics opioid abuse test is offered by Salugen® Biosciences, Inc., a Los Angeles biotechnology company that develops and markets proprietary laboratory tests to personalize pain medicine therapies. See Genetic testing for potential opioid abuse.
Home health care services	Recommended on a short-term basis following major surgical procedures or in-patient hospitalization, to prevent hospitalization, or to provide longer-term nursing care and supportive services for those whose condition is such that they would otherwise require inpatient care. Home health care is the provision of medical and other health care services to the injured or ill person in their place of residence. Home health services include both medical and non-medical services deemed to be medically necessary for patients who are confined to the home (homebound) and who require one or all of the following: 1). Skilled care by a licensed medical professional for tasks including, but not limited to, administration of intravenous drugs, dressing changes, occupational therapy, physical therapy, speech-language pathology services, and/or 2) Personal care services for health-related tasks and assistance with activities of daily living that do not require skills of a medical professional, such as bowel and bladder care, feeding, bathing, dressing and transfer and assistance with administration of oral medications, and/or (3) Domestic care services such as shopping, cleaning, and laundry that the individual is no longer capable of performing due to the illness or injury that may also be medically necessary in addition to skilled and/or personal care services. Domestic and personal care services do not require specialized training and do not need to be performed by a medical professional (ACMQ, 2005) (Ellenbecker, 2008).A prescription or request for authorization for home health services must include justification for medical necessity of the services. Justification for medical necessity requires the physician's documentation of: (1) The medical condition that necessitates home health services, including objective deficits in function

	and the specific activities precluded by such deficits; (2) The expected kinds of services that will be required, with an estimate of the duration and frequency of such services; and (3) The level of expertise and/or professional licensure required to provide the services. Homebound is defined as "confined to the home". To be homebound means: • The individual has trouble leaving the home without help (e.g., using a cane, wheelchair, walker, or crutches; special transportation; or help from another person) because of the occupational illness or injury **OR** Leaving the home isn't recommended because of the occupational illness or injury **AND** • The individual is normally unable to leave home and leaving home is a major effort (CMS, 2014). Evaluation of the medical necessity of home health care services is made on a case-by-case basis. For home health care extending beyond a period of 60 days, the physician's treatment plan should include referral for an in-home evaluation by a Home Health Care Agency Registered Nurse, Physical Therapist, Occupational Therapist, or other qualified professional certified by the Centers for Medicare and Medicaid in the assessment of activities of daily living to assess the appropriate scope, extent, and level of care for home health care services (CMS, 2015). The treating physician should periodically conduct re-assessments of the medical necessity of home health care services at intervals matched to the individual patient condition and needs, for example, 30, 60, 90, or 120 days. Such reassessments may include repeat evaluations in the home.
Homeopathic topicals	Not recommended for the treatment of chronic pain.
Horizontal therapy (HT)	See Interferential current stimulation (ICS).
Hospital length of stay (LOS)	Recommend the median length of stay (LOS) based on type of surgery, or best practice target LOS for cases with no complications. For prospective management of cases, median is a better choice that mean (or average) because it represents the mid-point, at which half of the cases are less, and half are more. For retrospective benchmarking of a series of cases, mean may be a better choice because of the effect of outliers on the average length of stay. Length of stay is the number of nights the patient remained in the hospital for that stay, and a patient admitted and discharged on the same day would have a length of stay of zero. The total number of days is typically measured in multiples of a 24-hour day that a patient occupies a hospital bed, so a 23-hour admission would have a length of stay of zero. (HCUP, 2011) Refer to the relevant Clinical Topics chapter of the MTUS for additional recommendations. **ODG hospital length of stay (LOS) guidelines:** **Sympathectomy** (*icd 05.29 -- Other sympathectomy and ganglionectomy*) Actual data -- median 1 day; mean 2.0 days (± 0.4); discharges 540; charges (mean) $24,544

	Best practice target (no complications) -- *Never recommended* **SCS** (*icd 03.93 Implantation or replacement of spinal neurostimulator leads*) Actual data -- median 1 day; mean 2.3 days (±0.2); discharges 3,998; charges (mean) $68,730 Best practice target (no complications) -- *1 day* *Note: About 14% of discharges paid by workers' compensation.* **Intrathecal Pump** (*icd 86.06 - Insertion of totally implantable infusion pump*) Actual data -- median 3 days; mean 5.4 days (±0.4); discharges 6,995; charges (mean) $62,325 Best practice target (no complications) -- *3 days* **Alcohol Detox** (*icd 94.62 - Alcohol detoxification*) Actual data -- median 3 days; mean 4.2 days (±0.1); discharges 169,797; charges (mean) $13,111 Best practice target (no complications) -- *3 days* **Alcohol Rehab/Detox** (*icd 94.63 - Alcohol rehabilitation and detoxification*) Actual data -- median 5 days; mean 7.0 days (±1.1); discharges 12,586; charges (mean) $12,166 Best practice target (no complications) -- *5 days* **Drug Detox** (*icd 94.65 - Drug detoxification*) Actual data -- median 4 days; mean 4.1 days (±0.2); discharges 78,219; charges (mean) $9,756 Best practice target (no complications) -- *4 days*
H-wave stimulation (HWT)	Not recommended as an isolated intervention for chronic pain but a one-month home-based trial may be considered as a noninvasive conservative option in accordance with the criteria below. There is insufficient evidence to recommend the use of H-wave stimulation (HWT) for the treatment of chronic pain as no high-quality studies on this topic were identified. If it is used, HWT is not recommended as an isolated intervention. 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. Two RCTs show reduction in pain and discomfort specifically associated with diabetic peripheral neuropathy (Kumar, 1997) (Kumar, 1998). Uncontrolled studies of HWT in patients with chronic soft tissue injury or neuropathic pain have reported reductions in pain and use of pain medication and improved functional capacity or activity. The patient selection criteria included unresponsiveness to physical therapy, medications, and TENS. (Blum, 2006) (Blum2, 2006) And a "meta-analysis" of predominantly these same uncontrolled studies indicated a moderate to strong effect of HWT in providing pain relief. (Blum, 2008) A randomized controlled trial, with identified risks of bias, demonstrated improved post-op range of motion following rotator cuff surgery, but the study could not draw a definitive conclusion concerning pain relief. (Blum, 2009) An ongoing double blinded randomized controlled trial with identified risks of bias is currently evaluating HWT in a working-age population with chronic non-specific low back pain. (Thiese, 2013) See also Interferential

current stimulation (ICS). For use recommendations related to the low back, see MTUS chapter on Low Back Complaints.
Other devices using the H-Wave name: The company Electronic Waveform Lab (EWL, Huntington Beach, CA) owns the trademark for H Wave® in the U.S. Another company, MIE Medical Research Ltd. (United Kingdom), sells an H-Wave therapy device (HWT) in the European market. This device is not approved by the FDA or available in the U.S. There are three published studies on this European device by McDowell et al. According to the first study, there is no evidence that HWT is more effective as an initial treatment when compared to TENS for analgesic effects. A randomized controlled trial of ischemic pain did not provide convincing evidence for any hypoalgesic effects of H-wave therapy. (McDowell, 1995) In another randomized controlled trial comparing analgesic effects of HWT and transcutaneous electrical nerve stimulation (TENS) on human pain thresholds, both HWT and TENS provided localized hypoalgesia during stimulation and for up to 5 minutes afterwards. No frequency- or modality-specific differences were found between the groups. (McDowell2, 1999) There is evidence that low-frequency HWT may produce direct localized effects on cutaneous blood flow. (McDowell, 1999) According to EWL, these are not the same devices as the H Wave® device available in the U.S.
How it works: The H-Wave® device uses output parameters and a waveform that are distinct from other electrical stimulation devices such as TENS. One mode of operation is intended to shut down pain by affecting the function of the sodium pump, while a second mode of operation is intended to improve recovery through increased blood flow and perfusion. Studies on the mechanisms of action of the H-Wave device demonstrated that it induces arteriolar vasodilation via nitric oxide-mediated mechanisms, increased blood flow and angiogenesis in test animals. (Smith, 2009) (Smith, 2011) In fact, H-wave may be used more often for muscle spasm and acute pain as opposed to chronic 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 therapy must be distinguished from the H-waves that are a component of electromyography. (BlueCross BlueShield, 2007) (Aetna, 2005

While not recommended as an isolated intervention, the following patient selection criteria should be documented by the medical care provider for H-wave stimulation (HWT) to be determined to be medically necessary:
(For use recommendations related to the low back, see MTUS chapter on Low Back Complaints.)
A. HWT may be considered on a trial basis if other noninvasive, conservative modalities for the treatment of chronic pain have failed. While medical providers may perform HWT, H-wave devices are also available for home use. Rental would be preferred over purchase during a home trial. Trial periods of more than one month should be justified by

	documentation submitted for review. B. Although there are no high quality studies to guide recommendations for use, a one-month home-based trial of HWT may be considered following a documented face-to-face clinical evaluation and physical examination performed by the recommending physician, who should also document the following in the medical record: (1) The reason the physician believes that HWT may lead to functional improvement and/or reduction in pain for the patient; and (2) PT, home exercise and medications have not resulted in functional improvement or reduction in pain; and (3) The use of TENS for at least a month has not resulted in functional improvement or reduction in pain. C. The one-month initial trial will permit the physician and PT provider to evaluate any effects and benefits. A follow-up evaluation by the physician should take place to document how often the unit was used and any subjective improvement in pain and function. There should be evidence of less reported pain combined with increased functional improvement or medication reduction D. If treatment is determined to be medically necessary, as with all other treatment modalities, the efficacy and continued need for this intervention should be periodically reassessed and documented.
Hydrocodone	See MTUS Opioids Treatment Guidelines for recommendations on the use of opioids. 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). Hydrocodone was reclassified to Schedule II effective October 6, 2014. (FDA 2014). The potency of hydrocodone, an active ingredient of the most commonly prescribed drug (of any type) in the U.S., is greater than morphine, an opioid that is a Schedule II substance. Schedule II drugs can be dispensed only by prescription, and no refills are allowed. Stringent record keeping, reporting, and physical security requirements are also in place for these substances. (FDA, 2013) See also Zohydro.
Hydrocodone/ Acetaminophen (e.g., Vicodin®, Lortab®)	See MTUS Opioids Treatment Guidelines on the use of opioids. Also see Hydrocodone/Acetaminophen (Anexsia®, Co-Gesic®, Hycet™; Lorcet®, Lortab®; Margesic-H®, Maxidone™; Norco®, Stagesic®, Vicodin®, Xodol®, Zydone®) listing for more information and references. An FDA advisory committee recommended a transition from Schedule III to Schedule II for hydrocodone products (FDA, 2013), but the DEA has yet to make any rules regarding rescheduling and still lists hydrocodone combination products as Schedule III. The Safe Prescribing Act proposed in U.S. Congress would legislatively reclassify hydrocodone combination products without going through the DEA. New York State made this transition to Schedule II in February 2013 as states have authority to upschedule. Now the DEA has officially proposed rescheduling of hydrocodone combination products from CIII to CII. (DEA, 2014) In this ED study, Vicodin failed to provide superior pain relief compared to Tylenol with codeine, and there was no significant difference in side effects. Both Vicodin and Hydrocodone decreased pain scores by approximately 50%, but hydrocodone/acetaminophen (Vicodin [5/500]) failed to provide

	clinically or statistically superior pain relief compared to codeine/acetaminophen (Tylenol#3 [30/300]). (Chang, 2014)
Hydrocodone/ Ibuprofen (Vicoprofen®)	See MTUS Opioids Treatment Guidelines for dosing recommendations. Also see Hydrocodone/Ibuprofen (Vicoprofen®) listing for more information and references.This combination opioid/NSAID has a low dose of ibuprofen (200mg) that is below the normal adult dose of 400 to 800 mg per dose and total max daily dose of 2400mg. Vicoprofen was approved only based on single dose, post-op pain and is approved to treat acute pain for generally less than 10 days. Prescribing information also stresses that this product is not indicated for treating conditions such as rheumatoid arthritis or osteoarthritis.) In addition, there is also a cost difference between the generic Vicodin (approx $0.35/tab) and generic Vicoprofen ($1.04/tab).
Hydromorphone (Dilaudid®)	See MTUS Opioids Treatment Guidelines for dosing recommendations. Also see Hydromorphone (Dilaudid®) listing for more information and references.
Hypnosis	Recommended as a conservative option, depending on the availability of providers with proven outcomes, but the quality of evidence is weak. Hypnosis treatment may have a positive effect on pain and quality of life for patients with chronic muscular pain. (Grøndahl, 2008) The findings of a trial supported greater benefits effects from self-hypnosis training compared to cognitive training on average pain intensity, but the combined hypnosis-cognitive restructuring intervention appeared to have beneficial effects greater than the effects of either cognitive restructuring or hypnosis alone. (Jensen, 2011) **ODG Hypnotherapy Guidelines:** - Initial trial of 4 visits over 2 weeks - With evidence of objective functional improvement, total of up to 10 visits over 6 weeks (individual sessions)
Hypnotics	See Benzodiazepines. See also Insomnia medications.
Ibuprofen (Motrin®, Advil®)	Recommended as an option. See Anti-inflammatory medications. See also NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Ibuprofen (Motrin®, Advil®) listing for more information and references.
Implantable drug-delivery systems/ Intrathecal drug delivery systems (IDDSs)	Recommended only as an end-stage treatment alternative for selected patients for specific conditions indicated in the blue criteria below, after failure of at least 6 months of less invasive methods, and following a successful temporary trial. See also MTUS Low Back Complaints. There is insufficient evidence to recommend the use of implantable drug-delivery systems (IDDS) for the treatment of chronic pain. There are no high-quality studies on this topic which document that this therapy is safe and effective. Further, significant complications and adverse events have been documented and the data identify a substantial risk to patients. (Washington State Health Care Authority, 2008) 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). This treatment may be considered 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) (Deer, 2009) (Patel, 2009) 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 or other intervention is not indicated, there are no contraindications to a trial, psychological evaluation unequivocally states that the individual has realistic expectations and 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) 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. (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 opioids, when administered in the long term, can be associated with problems such as tolerance 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) *Safety Precautions & Warnings:* Oral opioid prescribing, use and how to best keep patients as safe as possible have all have been the subject of increasing discussion, in part, due to related accidental deaths. (Phillips, 2008) Use of intrathecal opioids, as for all routes of administration, is not

	without risk. 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 granuloma formation, amenorrhea, loss of libido, edema, respiratory depression, death and pump and catheter malfunctions. (Winkelmuller, 1996) (Paice, 1997) (Washington State Health Care Authority#2, 2008) Common causes of mortality in implanted pump patients appear to be preventable through adherence to dosing and monitoring information for drugs approved for chronic intrathecal administration. Follow product instructions and dosing recommendations. Failure to comply with all implanted infusion pump product instructions can lead to technical errors or improper use and result in additional surgical procedures, a return of underlying symptoms, or a clinically significant drug underdose or fatal drug overdose. (Medtronic, 2009) The mortality rate in the implanted pump population is higher than some operative benchmarks and similar at approximately 30 days and 1-year post discharge to open spine surgery in the Medicare population. (Coffey, 2009) Patients who receive the implanted device should be monitored in an adequately equipped facility for a sufficient time to monitor drug effects. When using concomitant medications with respiratory or CNS depressant effects, appropriate supervision and monitoring should be provided. (Medtronic, 2009) *Patient selection* (in addition to criteria below): Cole (2003) recommends that, after other criteria are met, patients with neuropathic pain are better candidates for spinal cord stimulation (SCS), and patients with nociceptive pain are better candidates for intrathecal drug delivery (IDD). It also recommends psychological evaluation and clearance before any implantation, plus positive response to a trial. (Cole, 2003) **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 opioids or non-opioid 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 • A temporary trial of spinal (epidural or intrathecal) opioids 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 <u>non-malignant (non-cancerous) pain</u> with a duration of greater than 6 months and all of the following criteria are met and documented by treating providers in the medical record: 1. Non-opioid oral medication regimens have been tried and have failed to relieve pain and improve function (See MTUS Opioids Treatment Guidelines for a description of functional improvement); and 2. At least 6 months of other conservative treatment modalities (injection, surgical, psychologic or physical) have been ineffective in relieving pain and improving function; and 3. Intractable pain secondary to a disease state with objective documentation of pathology in the medical record (per symptoms, physicial examination, and diagnostic testing); and 4. Further surgical intervention or other treatment is not indicated or likely to be effective; and 5. Independent psychological evaluation has been obtained and evaluation states that the pain is not primarily psychologic in origin, the patient has realistic expectations and that benefit would occur with implantation despite any psychiatric comorbidity; and 6. No contraindications to implantation exist such as sepsis, spinal infection, anticoagulation or coagulopathy; and 7. There has been documented improvement in pain and function in response to oral opioid medications, but intolerable adverse effects preclude their continued use; and 8. 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 (intraspinal) infusion pumps is considered medically necessary only when criteria 1-7 above are met. 9. For average hospital LOS if criteria are met, see Hospital length of stay (LOS). If treatment is determined to be medically necessary, as with all other treatment modalities, the efficacy and continued need for this intervention and refills should be periodically reassessed and documented. **Medications for IDDS if determined to be medically necessary:** *First 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 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) The newer maximum concentrations were recommended, in part, to prevent granulomas. *Second 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) *Third 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). *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) According to the FDA, the manufacturer's manuals should be consulted for specific instructions and precautions for initial filling, refilling and programming. (FDA, 2010) For most pumps, the maximum dose that can be delivered between refills is 1000mg. If refills are usually administered after 16 to 17 mL have been infused, and most pumps are 18-20mL, the minimum time between each visit is 42 days if the daily dose rate is 20 mg/day. Given that a refill visit presents a good opportunity for monitoring, this panel suggested that the concentration be adjusted to allow refill visits a minimum of every 4 to 6 weeks, and maximum of every 2–3 months. (Bennett, 2000)
Implantable spinal cord stimulators	See Spinal Cord Stimulators (SCS).
Indomethacin	Not recommended. A large systematic review of available evidence on

(Indocin®, Indocin SR®)	NSAIDs confirms that naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk. Indomethacin is an older, rather toxic drug, and the evidence on cardiovascular risk should cast doubt on its continued clinical use. (McGettigan, 2011) See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Indomethacin (Indocin®, Indocin SR®) listing for more information and references. See also Tivorbex (indomethacin).
Injection with anaesthetics and/or steroids	See more specific modality. The following are choices: Epidural steroid injections (ESI's); Facet-joint injections; Lumbar sympathetic block; Trigger point injections; Stellate ganglion block; Prolotherapy; Piriformis injections; in this chronic pain guideline. *Pain injections general:* Consistent with the intent of relieving pain, improving function, decreasing medications, and encouraging return to work, repeat pain and other injections not otherwise specified, should at a very minimum relieve pain to the extent of 50% for a sustained period, and clearly result in documented reduction in pain medications, improved function, and/or return to work.
Insomnia	Recommend correcting deficits, as nonrestorative sleep is one of the strongest predictors for pain. Definition: Difficulty in sleep initiation or maintenance, and/or early awakening. Also characterized by impairment in daily function due to sleep insufficiency. These impairments include fatigue, irritability, decreased memory, decreased concentration, and malaise. Classifications: (1) *Based on symptoms:* Categories of symptoms include sleep onset, sleep maintenance, non-restorative sleep. These symptoms have been found to change over time. (2) *Based on duration:* (a) *Acute insomnia (transient insomnia):* Usually the result of specific environmental or social events. Generally treated by addressing the episode directly (death of a family member, working on a different shift, travel), or prophylactically. (b) *Chronic insomnia:* Generally defined as lasting more than one month. This condition may be correlated with other intrinsic sleep disorders, primary insomnia, or chronic medical conditions. Chronic insomnia is more likely to occur in the elderly, depressed patients, and medically ill populations. (3) *Based on etiology:* (a) *Primary insomnia:* No known physical or mental condition is noted as an etiology. This condition is generally consistent and responsive to treatment. (b) *Secondary insomnia (comorbid insomnia):* insomnia that is secondary to other medical and psychiatric illnesses, medications, or sleep disorders. Examples include chronic pain, gastroesophogeal reflux disease (GERD), heart failure, end-stage renal disease, diabetes, neurologic problems, psychiatric disorders, and certain medications. Diabetic patients appear to suffer insomnia due to alterations of circadian rhythm. They may also suffer from sleep disorders related to obesity. Psychiatric disorders associated with insomnia include depression, anxiety and alcoholism. (Reeder, 2007) (Benca, 2005) Poor or insufficient sleep is the strongest predictor for pain in adults over 50. Among factors associated with new-onset pain were: age (OR 0.97); baseline pain status (OR 1.1); anxiety (OR 1.5); physical health–related quality of life (OR 1.3); cognitive

	complaint (OR 1.3); & nonrestorative sleep (OR 1.9; 95% CI 1.2 - 2.8). This study points to the need to address underlying sleep problems to bring pain relief. (McBeth, 2014) See Insomnia treatment. See also Sleep studies.
Insomnia treatment	Recommend that treatment be based on the etiology, with the medications recommended below. See Insomnia. Pharmacological agents should only be used after careful evaluation of potential causes of sleep disturbance. Failure of sleep disturbance to resolve in a 7 to 10 day period may indicate a psychiatric and/or medical illness. (Lexi-Comp, 2008) Primary insomnia is generally addressed pharmacologically. Secondary insomnia may be treated with pharmacological and/or psychological measures. The specific component of insomnia should be addressed: (a) Sleep onset; (b) Sleep maintenance; (c) Sleep quality; & (d) Next-day functioning. ***Pharmacologic Treatment:*** There are four main categories of pharmacologic treatment: (1) Benzodiazepines; (2) Non-benzodiazepines; (3) Melatonin & melatonin receptor agonists; & (4) Over-the-counter medications. The majority of studies have only evaluated short-term treatment (i.e., ≤ 4 weeks) of insomnia; therefore more studies are necessary to evaluate the efficacy and safety of treatments for long-term treatment of insomnia. In 2007, the FDA requested that manufacturers of all sedative-hypnotic drugs strengthen product labeling regarding risks (i.e., severe allergic reactions and complex sleep-related behaviors, such as sleep driving). It is recommended that treatments for insomnia should reduce time to sleep onset, improve sleep maintenance, avoid residual effects and increase next-day functioning. (Morin, 2007) (Reeder, 2007) **(1) Benzodiazepines:** FDA-approved benzodiazepines for sleep maintenance insomnia include estazolam (ProSom®), flurazepam (Dalmane®), quazepam (Doral®), and temazepam (Restoril®). Triazolam (Halcion®) is FDA-approved for sleep-onset insomnia. These medications are only recommended for short-term use due to risk of tolerance, dependence, and adverse events (daytime drowsiness, anterograde amnesia, next-day sedation, impaired cognition, impaired psychomotor function, and rebound insomnia). These drugs have been associated with sleep-related activities such as sleep driving, cooking and eating food, and making phone calls (all while asleep). Particular concern is noted for patients at risk for abuse or addiction. Withdrawal occurs with abrupt discontinuation or large decreases in dose. Decrease slowly and monitor for withdrawal symptoms. Benzodiazepines are similar in efficacy to benzodiazepine-receptor agonists; however, the less desirable side-effect profile limits their use as a first-line agent, particularly for long-term use. (Holbrook, 2000) (Ramakrishnan, 2007) (Buscemi, 2007) (Morin, 2007) (Wafford, 2008) (Benca, 2005). **(2) Non-Benzodiazepine sedative-hypnotics (Benzodiazepine-receptor agonists):** First-line medications for insomnia. This class of medications includes zolpidem (Ambien® and Ambien® CR), zaleplon (Sonata®), and eszopicolone (Lunesta®). Benzodiazepine-receptor agonists work by selectively binding to type-1 benzodiazepine receptors in the CNS. All of the benzodiazepine-receptor agonists are schedule IV controlled substances, which means they have potential for abuse and dependency. Although direct comparisons between

	benzodiazepines and the non-benzodiazepine hypnotics have not been studied, it appears that the non-benzodiazepines have similar efficacy to the benzodiazepines with fewer side effects and short duration of action. (Ramakrishnan, 2007) (Halas, 2006) (Buscemi, 2007) (Morin, 2007) (Erman, 2005) ***Zolpidem*** *[Ambien® (generic available), Ambien CR™]* is indicated for the short-term treatment of insomnia with difficulty of sleep onset (7-10 days). Ambien CR is indicated for treatment of insomnia with difficulty of sleep onset and/or sleep maintenance. Longer-term studies have found Ambien CR to be effective for up to 24 weeks in adults. (Buscemi, 2005) (Ramakrishnan, 2007) (Morin, 2007). The extended-release dual-layer tablet (Ambien CR™) has a biphasic release system; an initial release of zolpidem reduces sleep latency and a delayed release facilitates sleep maintenance. *Side effects:* headache, daytime drowsiness, dizziness, blurred vision, confusion, abnormal thinking and bizarre behavior have occurred. Sleep driving and other activities for which the patient has no recollection may occur. The medication should be discontinued if the latter occurs. Abrupt discontinuation may lead to withdrawal. *Dosing:* Ambien 5 to 10 mg at bedtime (5 mg in women, the elderly and patients with hepatic dysfunction); Ambien CR 6.25 to 12.5 mg at bedtime (6.25 mg in women, the elderly and patients with hepatic dysfunction) (Morin, 2007). Adults who use zolpidem have a greater than 3-fold increased risk for early death, according to results of a large matched cohort survival analysis. (Kripke, 2012) Due to adverse effects, FDA now requires lower doses for zolpidem. The dose of zolpidem for women should be lowered from 10 mg to 5 mg for IR products (Ambien, Edluar, Zolpimist, and generic) and from 12.5 mg to 6.25 mg for ER products (Ambien CR). (FDA, 2013) See also Zolpidem. ***Zaleplon*** *(Sonata®)* reduces sleep latency. *Side effects:* headache, drowsiness, dizziness, fatigue, confusion, abnormal thinking. Sleep-related activities have also been noted such as driving, cooking, eating and making phone calls. Abrupt discontinuation may lead to withdrawal. *Dosing:* 10 mg at bedtime (5 mg in the elderly and patients with hepatic dysfunction). (Morin, 2007) Because of its short half-life (one hour), may be readministered upon nocturnal wakening provided it is administered at least 4 hours before wake time. (Ramakrishnan, 2007) This medication has a rapid onset of action. Short-term use (7-10 days) is indicated with a controlled trial showing effectiveness for up to 5 weeks. ***Eszopicolone*** *(Lunesta™)* has demonstrated reduced sleep latency and sleep maintenance. (Morin, 2007) The only benzodiazepine-receptor agonist FDA approved for use longer than 35 days. A randomized, double blind, controlled clinical trial with 830 primary insomnia patients reported significant improvement in the treatment group when compared to the control group for sleep latency, wake after sleep onset, and total sleep time over a 6-month period. (Walsh, 2007) *Side effects:* dry mouth, unpleasant taste, drowsiness, dizziness. Sleep-related activities such as driving, eating, cooking and phone calling have occurred. Withdrawal may occur with abrupt discontinuation. *Dosing:* 1-2 mg for difficulty falling asleep; 2-3 mg for sleep maintenance. The drug has a rapid onset of action. (Ramakrishnan, 2007) ***Sedating antidepressants*** (e.g., amitriptyline, trazodone, mirtazapine) have also been used to treat insomnia; however, there is less

	evidence to support their use for insomnia (Buscemi, 2007) (Morin, 2007), but they may be an option in patients with coexisting depression. (Morin, 2007) Trazodone is one of the most commonly prescribed agents for insomnia. Side effects of this drug include nausea, dry mouth, constipation, drowsiness, and headache. Improvements in sleep onset may be offset by negative next-day effects such as ease of awakening. Tolerance may develop and rebound insomnia has been found after discontinuation. **(3) Melatonin-receptor agonist: *Ramelteon (Rozerem™)*** is a selective melatonin agonist (MT_1 and MT_2) indicated for difficulty with sleep onset; is nonscheduled (has been shown to have no abuse potential). One systematic review concluded that there is evidence to support the short-term and long-term use of ramelteon to decrease sleep latency; however, total sleep time has not been improved. (Reynoldson, 2008) (Zammit, 2007) Ramelteon is not a controlled substance. *Side effects:* CNS depression, somnolence, dizziness, fatigue, abnormal thinking and bizarre behavior have occurred. Use with caution in patients with depression, hepatic impairment, and respiratory conditions such as COPD or sleep apnea. *Dosing:* 8mg within 30 minutes of bedtime; recommended for short-term (7 – 10 days) use only. **(4) Over-the-counter medications:** Sedating antihistamines have been suggested for sleep aids (for example, diphenhydramine). Tolerance seems to develop within a few days. Next-day sedation has been noted as well as impaired psychomotor and cognitive function. Side effects include urinary retention, blurred vision, orthostatic hypotension, dizziness, palpitations, increased liver enzymes, drowsiness, dizziness, grogginess and tiredness. ***Non-pharmacologic treatment:*** Empirically supported treatment includes stimulus control, progressive muscle relaxation, and paradoxical intention. Treatments that are thought to probably be efficacious include sleep restriction, biofeedback, and multifaceted cognitive behavioral therapy. **Suggestions for improved sleep hygiene:** (a) Wake at the same time every day; (b) Maintain a consistent bedtime; (c) Exercise regularly (not within 2 to 4 hours of bedtime); (d) Perform relaxing activities before bedtime; (e) Keep your bedroom quiet and cool; (f) Do not watch the clock; (g) Avoid caffeine and nicotine for at least six hours before bed; (h) Only drink in moderation; & (i) Avoid napping. (Benca, 2005) In a head-to-head comparison of treatment approaches to determine separate and combined effects on insomnia, adding a prescription sleeping pill to cognitive behavioral therapy (CBT) appeared to be the optimal initial treatment approach in patients with persistent insomnia, but after 6 weeks, tapering the medication and continuing with CBT alone produced the best long-term outcome. These results suggest that there is a modest short-term added value to starting therapy with CBT plus a medication, especially with respect to total sleep gained, but that this added value does not persist. In terms of first-line therapy, for acute insomnia lasting less than 6 months, medication is probably the best treatment approach, but for chronic insomnia, a combined approach might give the best of both worlds; however, after a few weeks, the recommendation is to discontinue the medication and continue with CBT. Prescribing medication indefinitely will not work. The authors said that the conclusion that patients do better in the long-term if medication is stopped after 6 weeks and only CBT is continued

	during an additional 6-month period is an important new finding. (Morin, 2009)
Integrative manual therapy (IMT™)	See Chronic pain programs. Integrative Manual Therapy (IMT™) is a proprietary type of multidisciplinary chronic pain program with a unique set of techniques, approaches, and methodologies that address pain, dysfunction, disease and disability. The treatment approach is multidisciplinary and includes physical therapy, manual therapy, nutrition, and psychology, and involves specific proprietary training. (Giammatteo, 2013) There are no recommendations for this type of therapy as there are no published high-quality studies specific to IMT. See the *Criteria for the general use of multidisciplinary pain management programs*, under Chronic pain programs.
Interdisciplinary rehabilitation programs	See Chronic pain programs.
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 knee pain. (Van der Heijden, 1999) (Werners, 1999) (Hurley, 2001) (Hou, 2002) (Jarit, 2003) (Hurley, 2004) (CTAF, 2005) (Burch, 2008, 2008) The findings from these trials were either negative or insufficient for recommendation due to poor study design and/or methodologic issues. In addition, 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 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 from TENS:* It has been postulated that ICS 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 ICS. *Current recommendations:* Health plans have taken a variety of positions with respect to ICS. See H-wave stimulation (HWT), and Interferential current stimulation. *California Technology Assessment Forum* concluded that 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 *Blue Cross/Blue Shield* 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, the following patient selection criteria should be documented by the medical care provider for Interferential Current Stimulation to be determined medically necessary:** Possibly appropriate for the following conditions if it has been documented and proven to be effective as directed or applied by the physician or a provider licensed to provide physical therapy:

	- 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 or acute conditions limits the ability to perform exercise programs/physical therapy treatment; or - Unresponsive to conservative measures (e.g., repositioning, heat/ice, medications, etc.). If those criteria are met, then a one-month trial may be appropriate to permit the physician and physical therapy 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. If treatment is determined to be medically necessary, as with all other treatment modalities, the efficacy and continued need for this intervention should be periodically reassessed and documented. Treatment of unlimited duration is not recommended.
Internal qigong	Not recommended. This review of controlled clinical trials focused on the effects of internal qigong, a self-directed energy healing intervention involving movement and meditation. Collectively, the existing trial evidence is not convincing enough to suggest that internal qigong is an effective modality for pain management. (Lee, 2009) Qi Gong or Qigong is a traditional Chinese medicine technique. There are two types of qigong: internal and external. Internal qigong techniques include learned and self-directed exercises that involve sounds, movements and meditation. External qigong (Qi emission) is practiced by a Qi Gongmaster who uses his or her hands with the aim to project qi ("chi") to others for the purpose of healing. In traditional Chinese medicine, qigong is considered beneficial for a large variety of medical conditions. Many practitioners believe there is a role for qigong in treating chronic conditions such as cancer, chronic fatigue syndrome, osteoporosis, high blood pressure, stomach ulcers and asthma. There is early research supporting the use of internal qigong exercises or externally applied Qi for pain management and reduction of anxiety associated with pain. More evidence is needed before a firm recommendation can be made. Qigong is generally believed to be safe when practiced appropriately, but it should not be used as the sole treatment for severe illnesses, and people with psychiatric disorders should only practice qigong under supervision.
Intrathecal drug delivery systems (IDDSs)	See Implantable drug delivery systems (IDDSs).
Intrathecal pumps	See Implantable drug-delivery systems (IDDSs).
Intravenous regional sympathetic blocks (for RSD/CRPS)	Not recommended due to lack of evidence for use. There is no role for IV diagnostic blocks with phentolamine or IVRA with guanethidine. Other procedures include IV regional blocks with lidocaine, lidocaine-methyl-prednisolone, droperidol, ketanserin, atropine, bretylium, clonidine, and reserpine. If used, there must be evidence that the Budapest criteria have

	been met and all other diagnoses have been ruled out. Evidence of sympathetically mediated pain should be provided. The reason for the necessity of this procedure over-and-above a standard sympathetic block should also be provided. (Perez, 2010) (Harden, 2013) (Tran, 2010) See also CRPS, sympathetic blocks (therapeutic).
Kadian® (morphine sulfate)	See MTUS Opioids Treatment Guidelines for recommendations on the use of opioids. According to the FDA approved prescribing information, "*Use of Kadian as the First Opioid Analgesic:"* There has been no evaluation of Kadian as an initial opioid analgesic in the management of pain. (FDA, 2010) Kadian is not for use as an as-needed (PRN) analgesic. It is not for use for pain that is mild or not expected to persist for an extended period of time. It is not for use for acute pain and not for use for postoperative pain unless the patient is already receiving chronic opioid therapy. *Dosing:* There is no data to support the use of Kadian more than every 12 hours. *Comparison to use of other extended-release morphine formulations:* Research has shown no significant difference between Kadian (in 24 and 12 hour dosing duration) as compared to MS Contin treatment of cancer pain in terms of or safety. (Broomhead, 1997) (Gourlay 1997) *Bioequivalence:* As per the Package Insert, Kadian is not bioequivalent to other extended-release morphine preparations. The slower release of morphine may result in reduced maximum and increased minimum plasma morphine concentrations than with shorter acting morphine products. Conversion to other extended-release morphine preparations may lead to either excessive sedation at peak or inadequate analgesia at trough. The FDA Orange Book (accessed March 2013) has determined that actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence.
Ketamine	Not recommended. There is insufficient evidence to support the use of ketamine for the treatment of CRPS. Current studies are experimental and there is no consistent recommendation for protocols, including for infusion solutions (in terms of mg/kg/hr), duration of infusion time, when to repeat infusions, how many infusions to recommend, or what kind of outcome would indicate the protocol should be discontinued. The safety of long-term use of the drug has also not been established, with evidence of potential of neurotoxicity. Ketamine-induced liver toxicity is a major risk, occurring up to 50% of the time, and regular measures of liver function are therefore required during such treatments. (Noppers, 2011) Frequent use can cause long-term memory impairment and altered pre-frontal dopaminergic function. (Morgan, 2012) Ketamine is also known as a drug of abuse. Abuse of ketamine can cause cystitis and a contracted bladder, and secondary renal damage can occur in severe cases which might be irreversible, rendering patients dependent on dialysis. (Chu, 2008) (Morgan, 2012) There is no evidence of a cure of CRPS with subanesthetic infusions. The limited results of current research studies on this topic are inconsistent. An early successful retrospective report of 33 patients documented that 54% of patients experienced greater than 3 months of pain relief, with 31% experiencing greater than 6 months of relief. The authors reported the long-term effects of ketamine infusion were unknown and could include neurotoxicity and hepatic dysfunction. (Correll,

	2004) Subsequent non-controlled studies have found less impressive findings (using probability statistics due to lack of long-term follow-up of 41% of patients), predicting a 13% to 31% chance of relief lasting more than three weeks. (Patil, 2011) Another study has shown decreased pain scores but no functional improvement. (Sigtermans, 2009) The overall current recommendation is that larger randomized placebo controlled trials occur, looking at dosing and long-term follow-up. (Schwartzman, 2009) Subcutaneous ketamine used as an adjunct to opioids for neuropathic and nociceptive pain provides no benefit and increases adverse events significantly, according to this double-blind RCT. (Hardy, 2012)
Ketoprofen	Recommended as an option. See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Ketoprofen listing for more information and references.
Ketoprofen, topical	Not recommended in the U.S., as there are currently no FDA-approved versions of this product, but it is a first-line drug in Europe. See Topical analgesics, Non-steroidal antinflammatory agents (NSAIDs), and the ketoprofen topical listing, for more information and references. Topical NSAIDs are generally recommended for short-term use for acute sprain/strains and longer term for osteoarthritis of the knee and hand, particularly in individuals with risk for GI ulceration, but they are not indicated for treatment of the low back or neuropathic pain. At this time, the only available FDA-approved topical NSAID is diclofenac, but recent high-quality studies have identified a dangerous increased risk profile with diclofenac, including topical formulations, making it a second-line recommended treatment in ODG. Topical ketoprofen has been approved by the European FDA (the European Medicines Agency), and the European EULAR and NICE guidelines state these approved formulations of topical ketoprofen should be a first-line treatment, and should be considered before oral NSAIDs because they have shown efficacy significantly superior to placebo and similar to oral NSAIDs, without the same risks of adverse effects. While there are no FDA approved formulations of topical ketoprofen available in the U.S., the product is available from compounding pharmacies. Compound medications are not FDA approved, but they are allowed under state pharmacy regulations. See Compound drugs. Because each compounding pharmacy may create their own version, FDA cannot be a source of information on safety and effectiveness of each version, or on generic equivalency. At this time, there are no high-quality studies of any of the various pharmacy compounded formulations of topical ketoprofen available in the U.S. Also, while topical ketoprofen has been used extensively in Europe, in 2009 France removed this product from the market due to photosensitivity reactions. The drug has been reinstated, but this may be a serious problem. See the ketoprofen topical listing in Topical analgesics, Non-steroidal antinflammatory agents.
Ketorolac (Toradol®)	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as

	well as specific Ketorolac (Toradol®) listing for more information and references, where it is indicated that the oral formulation should not be given as an initial dose, but only as continuation following IV or IM dosing. Ketorolac, when administered intramuscularly, may be used as an alternative to opioid therapy. (DeAndrade, 1994)
Lacosamide (Vimpat®)	Not recommended as a first-line therapy for use in neuropathic pain. Lacosamide (Vimpat) is a novel antiepileptic medication that is approved only for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy. Despite a number of clinical studies conducted to evaluate lacosamide efficacy and safety in treating diabetic peripheral neuropathy, the FDA has declined to approve this indication. There are a number of safety concerns related to lacosamide, including second and third degree AV block, atrial fibrillation and flutter, and neurotoxicity. (O'Lenic, 2012)
Lamotrigine (Lamictal®)	See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Lamotrigine listing.
Lazanda (fentanyl nasal spray)	See MTUS Opioids Treatment Guidelines .
Levetiracetam (Keppra®)	See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Levetiracetam listing.
Lidocaine (anesthetic)	Lidocaine is a local anesthetic. See CRPS, medications; CRPS, sympathetic and epidural blocks; Topical analgesics.
Lidoderm® (lidocaine patch)	Not recommended until after a trial of a first-line therapy, according to the criteria below. Lidoderm® is the brand name for a lidocaine patch produced by Endo Pharmaceuticals. Topical lidocaine may be recommended for localized neuropathic 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). This is not a first-line treatment and is only FDA approved for 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. **Criteria for use of Lidoderm patches:** (a) Recommended for a trial if there is evidence of localized pain that is consistent with a neuropathic etiology. (b) There should be evidence of a trial of first-line neuropathy medications (tri-cyclic or SNRI anti-depressants or an AED such as gabapentin or Lyrica). (c) This medication is not generally recommended for treatment of osteoarthritis or treatment of myofascial pain/trigger points. (d) An attempt to determine a neuropathic component of pain should be made if the plan is to apply this medication to areas of pain that are generally secondary to non-neuropathic mechanisms (such as the knee). One recognized method of testing is the use of the Neuropathic Pain Scale. (e) The area for treatment should be designated as well as number of planned patches and duration for use (number of hours per day). (f) A Trial of patch treatment is recommended for a short-term period (no more than four weeks).

	(g) It is generally recommended that no other medication changes be made during the trial period. (h) Outcomes should be reported at the end of the trial including improvements in pain and function, and decrease in the use of other medications. If improvements cannot be determined, the medication should be discontinued. (i) Continued outcomes should be intermittently measured and if improvement does not continue, lidocaine patches should be discontinued.
Limbrel (flavocoxid)	Not recommended for treatment of chronic pain. See Medical foods.
Lorazepam	Not recommended. See Benzodiazepines.
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, see use of red-beam or near-infrared lasers with a wavelength between 600 and 1000 nm and Watts 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)
Lubiprostone (Amitiza®)	Recommended only as a possible second-line treatment for opioid-induced constipation. See Opioid-induced constipation treatment.
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)
Lunesta (Eszopicolone)	See Eszopicolone (Lunesta).
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) (Maher, 2004) (BlueCross BlueShield, 2005)
Manual therapy & manipulation	Manual therapy and manipulation, performed by a variety of practitioners, including physical therapists and chiropractors, are passive interventions that are typically combined with recommended treatment, especially active interventions (e.g., exercise). Recommended for chronic pain if caused by musculoskeletal conditions, and only when manipulation is specifically recommended by the provider in the plan of care. Manual Therapy is widely used in the treatment of musculoskeletal pain with the intended goal 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. Manipulation under anesthesia is not recommended. See also specific body-part chapters in the MTUS. **Recommended treatment parameters**: a. Time to produce effect: 4 to 6 treatments. b. Frequency: 1 to 2 times per week for 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 MMI 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.
Marijuana	See Cannabinoids.
Massage therapy	Recommended as an option as indicated below. Massage is a passive intervention and is considered an adjunct to other recommended treatment, especially active interventions (e.g., exercise). 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. . 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) The efficacy of massage as a stand-alone and as multimodality treatment is uncertain, according to this Cohrane review. (Haraldsson, 2007) A recent meta-analysis concluded that massage might be beneficial for patients with subacute and chronic non-specific low-back pain, especially when combined with exercises and education. When massage was compared to an inert therapy (sham treatment), massage was superior for pain and function on both short and long-term follow-ups. When massage was compared to other active treatments, massage was similar to exercises, and massage was superior to joint mobilization, relaxation therapy, physical therapy, acupuncture and self-care education. Reflexology on the feet had no effect on pain and functioning. The beneficial effects of massage in patients with chronic low-back pain lasted at least one year after the end of the treatment. In comparing different techniques of massage, acupuncture massage produced better results than classic (Swedish) massage and Thai massage produced similar results to classic

	(Swedish) massage. (Furlan-*Cochrane*, 2008) A small controlled study showed that 10 minutes of massage therapy can help repair exercise-induced muscle damage by subduing inflammation and renewing mitochondria, similar to the way NSAIDs work. The findings suggest that the perceived positive effects of massage are a result of an attenuated production of inflammatory cytokines. (Crane, 2012) **Recommended frequency and duration of treatment:** Time to Produce Effect: Immediate. Frequency: 1 to 2 times per week. Optimum Duration: 6 weeks. Maximum Duration: 2 months. (Colorado, 2006) At 2 months, patients should be reevaluated. Care beyond 2 months may be indicated for certain chronic pain patients in whom massage 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 MMI 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 2 months should be documented with objective improvement in function. Palliative care should be reevaluated and documented at each treatment session. Injured workers with complicating factors may need more treatment, if functional improvement is documented by the treating physician.
Medical foods	Medical foods and dietary supplements are not recommended for treatment of chronic pain as they have not been shown to produce meaningful benefits or improvements in functional outcomes. FDA defines a medical food as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." There are no quality studies demonstrating the benefit of medical foods in the treatment of chronic pain. Medical foods (defined in section 5(b)(3) of the Orphan Drug Act, 21 U.S.C. 360ee(b)(3)), are exempted from the labeling requirements for health claims and nutrient content claims under the Nutrition Labeling and Education Act of 1990 (see 21 U.S.C. 343 (q) (5) (A) (iv)). Medical foods do not have to be registered with the FDA. (CFSAN, 2008)
Medical marijuana	See Cannabinoids.
Medications for acute pain (analgesics)	Recommended as indicated below. *Acetaminophen* is the initial choice for treatment of acute pain & acute exacerbations of chronic pain in a dose of 1,000 mg. A recent study found that in a single dose, aspirin was similar to acetaminophen (mg to mg comparison) for treatment of acute pain, although aspirin is more likely to produce GI side effects. (Edwards, 2006) (Sachs, 2005) To help encourage appropriate acetaminophen use, the makers of Extra Strength Tylenol® (acetaminophen) have implemented new dosing instructions lowering the maximum daily dose from 4,000 mg to 3,000 mg. (McNeil,

	2012) There should be caution about daily doses of acetaminophen and liver disease if over 4,000 mg per day or in combination with other NSAIDs. (Watkins, 2006) A 2008 Cochrane review found that NSAIDs are not more effective than acetaminophen for acute low-back pain, but acetaminophen had fewer side effects, which support recommending NSAIDs as a treatment option after acetaminophen. (Roelofs-Cochrane, 2008) *NSAIDs* are superior to acetaminophen for some types of pain, and can provide analgesia similar to opioids in some settings, including post-operatively. (Mason, 2006) An important concern is side effects such as GI disturbance, renal dysfunction, increased edema, and increased blood pressure. NSAIDs, and the Cox-2 NSAIDS in particular, also are associated with thrombotic cardiovascular events. *Opioids:* See MTUS Opioids Treatment Guidelines for recommendations on the use of opioids.
Medication overuse headache	*Definition:* (1) Headache present on ≥ 15 days a month; (2) Regular overuse for ≥ 3 months of acute treatment of symptomatic treatment drugs including opioids, combination analgesics, triptans or ergotamines (one or more of these drugs); (3) Use of these same medications on ≥ 15 days a month or a regular basis for ≥ 3 months (with no overuse of any one class alone); & (4) headache that is worse during medication overuse. The prevalence of this condition may be as high as 59-64% of patients seen in tertiary headache centers in the US. A risk factor for this condition is frequent to daily use of analgesics for chronic neck pain (RR=2.2) and chronic low back pain (RR=2.3). Other risks include the use of opioids for other medical conditions, psychiatric comorbidity, dependence on other psychoactive substances (including alcohol and nicotine), and a family history of substance abuse. *Recommended treatment:* Includes screening for medication usage via the following: interviews with the patient; interviews with other family members; contact with prescribing physicians; and pharmacy billing records. Urine drug screens are also recommended. Complex cases may require both medical and behavioral intervention. (Lake, 2008) (Olesen, 2006)
Medrol dose pack	See Oral corticosteroids.
Mefenamic Acid (Ponstel®)	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Mefenamic Acid (Ponstel®) listing for more information and references.
Melatonin	Recommended. See Insomnia treatment. There are also experimental and clinical data supporting an analgesic role of melatonin. In published studies melatonin shows potent analgesic effects in a dose-dependent manner, and melatonin has been shown to have analgesic benefits in patients with chronic pain. Also, the repeated administration of melatonin improves sleep and thereby may reduce anxiety, which leads to lower levels of pain. (Wilhelmsen, 2011)
Meloxicam (Mobic®)	Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) for the relief of the signs and symptoms of osteoarthritis. See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk;

	NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific meloxicam (Mobic®) listing for more information and references. A large systematic review of available evidence on NSAIDs confirms that naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk. In the pooled analyses, meloxicam had a risk profile similar to that of ibuprofen and celecoxib. (McGettigan, 2011)
Meperidine (Demerol®)	See MTUS Opioids Treatment Guidelines for recommendations on the use of opioids. Meperidine is an opioid analgesic, similar to morphine, and has been used to relieve moderate to severe pain. The AGS updated Beers criteria for inappropriate medication use includes meperidine. (AGS, 2012)
Meprobamate	Meprobamate is the active metabolite of carisoprodol. See Carisoprodol (Soma®).
Metaxalone (Skelaxin®)	Recommended with caution as a second-line option for acute LBP and 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	See MTUS Opioids Treatment Guidelines for recommendations on use. Methadone is used as a second-line drug for moderate to severe pain, only if the potential benefit outweighs the risk, unless methadone is prescribed by pain specialists with experience in its use and by addiction specialists, *Pharmacokinetics and pharmacodynamics:* Increased morbidity and mortality appears, in part, secondary to the long and variable half-life of the drug (8-59 hours; up to 110 hours in patients with cancer). Pain relief on the other hand only lasts from 4-8 hours. It may take several days to weeks to obtain adequate pain control. 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. Frequent or large dose changes are generally not necessary after initial titration. If analgesia is lost, this may reflect the addition of a medication that affects metabolism. (Weschules 2008) (Fredheim 2008) *Adverse effects and mortality:* Methadone-related deaths are noted to be increasing at a faster rate than other poisoning deaths using data from the National Center for Health Statistics, increasing by 468% from 1999 to 2005 (total poisoning deaths increased by 66%). Methadone-related poisoning deaths had the greatest percentage increase of deaths compared with other opioids, although the actual number of deaths is less than from other opioids or cocaine. The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System found that from 2003 until 2006 patients that filled prescriptions for methadone had the highest fatal poisoning rate for all people filling prescriptions. Approximately 35% of methadone deaths were characterized as resulting from an abuse situation. Two-thirds involved use of multiple drugs including antidepressants, alcohol and cocaine. Deaths can also occur with too rapid titration. Delayed adverse effects may occur due to methadone accumulation during chronic administration. (Fingerhut, 2008) (Dart, 2007)

	(Center for Substance Abuse Treatment, 2009) 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 NMDA receptor antagonism properties. 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). *Abuse potential:* Methadone does have the potential for abuse. "Street methadone" is primarily used for self-medication of detoxification and withdrawal symptoms. According to CDC, methadone has played a central role in the increase in overdose deaths from prescription painkillers. More than 30% of prescription painkiller deaths involve methadone, even though only 2% of painkiller prescriptions are for this drug. Six times as many people died of methadone overdoses in 2009 than a decade before. (CDC, 2012) *Cardiac safety and EKG monitoring:* Methadone use is associated with an increased risk for QT prolongation and torsade de pointes (TdP). Patients who are at most risk for TdP include those on high daily methadone doses, those who take medications that cause QTc prolongation or inhibit CYP34A enzymes, and patients with electrolyte imbalances (low magnesium or potassium).
Methylnaltrexone (Relistor®)	Recommended only as a possible second-line treatment for opioid-induced constipation. See Opioid-induced constipation treatment.
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)
Midazolam	Not recommended. See Benzodiazepines.
Milnacipran (Savella®)	Not recommended for chronic pain. An FDA Phase III study demonstrated "significant therapeutic effects" of milnacipran for treatment of fibromyalgia syndrome. Milnacipran has been approved for the treatment of depression outside of the U.S. and is a dual serotonin- and norepinephrine-reuptake inhibitor (SNRI). (Rooks, 2007) Milnacipran, one of the pioneer serotonin and norepinephrine reuptake inhibitors (SNRIs), was designed from theoretic considerations to be more effective than selective serotonin reuptake inhibitors (SSRIs) and better tolerated than tricyclic antidepressants (TCAs). (Kasper, 2010) FDA has now approved milnacipran (Savella) for the management of fibromyalgia. Milnacipran should be prescribed with caution in patients with a history of seizure disorder, mania, or controlled narrow-angle glaucoma and should ordinarily not be prescribed in patients with substantial alcohol use or evidence of chronic liver disease. (FDA, 2009) As there is little to no evidence that the cause of fibromyalgia is related to industrial injuries, the use of Savella should be restricted to documented cases of fibromyalgia

	as part of an appropriate treatment plan.
Mindfulness meditation	See Yoga & Mindfulness meditation.
Mobic® (meloxicam)	Mobic is a brand name for meloxicam supplied by Boehringer Ingelheim Pharmaceuticals, Inc. See Meloxicam (Mobic®).
Modafinil (Provigil®)	Not recommended solely to counteract sedation effects of narcotics until after first considering reducing excessive narcotic prescribing. Use with caution as indicated below. *Indications:* Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder. Patients should have a complete evaluation with a diagnosis made in accordance with the International Classification of Sleep Disorders or DSM diagnostic classification. *Adverse effects:* This drug has been known to be misused and/or abused, particularly by patients that have a history of drug or stimulant abuse. Common adverse effects include headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. *Dose:* The standard dose for these conditions is 200 mg a day. The dose should be reduced to ½ for patients with severe hepatic impairment. (Clinical Pharmacology, 2008) (Micromedix, 2008) (Lexi-Comp, 2008) (AHFS Drug Information, 2008) Modafinil is increasingly being used as a cognitive enhancer. Although initially launched as distinct from stimulants that increase extracellular dopamine by targeting dopamine transporters, recent preclinical studies suggest otherwise. There is need for heightened awareness for potential abuse of and dependence on modafinil. (Kumar, 2008) (Volkow-*JAMA*, 2009) Prescriptions for modafinil have rapidly increased in recent years, and most of this increase is due to off-label use, according to a JAMA study, with 89% of patients prescribed modafinil not having an on-label diagnosis. The company that markets modafinil, Cephalon Inc, was sued by several US states for promoting modafinil for off-label indications and agreed to a settlement in 2008. (Peñaloza, 2013)
Monofilament testing	Not recommended. The sole use of monofilament testing is not recommended to diagnose peripheral neuropathy, according to the results of a recent systematic review. Several tests are used to detect peripheral neuropathy, including vibration perception, application of warmth and cold, and nerve conduction studies, which are assumed to be the reference standard. Electrodiagnostic tests can be complex, expensive, and time consuming, which hampers their widespread use, especially in primary care, where for most patients peripheral neuropathy is diagnosed and treated. Monofilament testing is an inexpensive, easy-to-use, and portable test for assessing the loss of protective sensation, and it is recommended by several practice guidelines to detect peripheral neuropathy in otherwise normal feet. Sensitivity of the 5.07/10-g monofilament to detect peripheral neuropathy ranged from 41% to 93%, and specificity ranged from 68% to 100%. Despite the frequent use of monofilament testing, little can be said about the test accuracy for detecting neuropathy in feet without visible ulcers. The diagnosis of peripheral neuropathy can be made only after a careful clinical examination with more than 1 test, as recommended by the American Diabetes Association. Tests for this clinical examination are

	vibration perception (using a 128-Hz tuning fork), pressure sensation (using a 10-g monofilament at least at the distal halluces), ankle reflexes, and pinprick. When in doubt, a nerve conduction test might be necessary to establish a firm diagnosis. (Dros, 2009)
Morphine	See specific morphine sulfate (MS Contin®; Avinza®; Kadian®; Oramorph SR®) listing for more information and references, or by the brands: Avinza; Kadian & Oramorph. See MTUS Opioids Treatment Guidelines, Appendix F1, for dosing recommendations.
Morphine pumps	*See* Implantable drug-delivery systems/ Intrathecal drug delivery systems (IDDSs).
MS Contin®	See Morphine.
MSM (methylsulfonylmethane)	See CRPS, medications, DMSO.
Multidisciplinary pain programs	See Chronic pain programs.
Muscle relaxants (for pain)	Refer to the relevant Clinical Topics section of the MTUS for recommendations. Muscle relaxants may be effective in reducing pain and muscle tension, and increasing mobility. 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. (Schnitzer, 2004) (Van Tulder, 2004) (Airaksinen, 2006) 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) **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 $GABA_B$ 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®, Fexmid™, generic available, ER as Amrix®): Recommended for a short course of therapy. Immediate release (eg, Flexeril, generic) recommended over extended release (Amrix) due to recommended short course of therapy (also note substantial increase in cost for extended release without corresponding benefit for 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) A recent RCT found that time to relief was better with immediate release compared to extended release cyclobenzaprine. (Landy, 2011)
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)
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™DS, 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):** Not recommended in ODG. Suggested by the manufacturer for use as an adjunct to rest, physical therapy, analgesics, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. (AHFS, 2008) A 250 mg formulation was FDA approved in 9/07 for treatment of acute, painful musculoskeletal conditions such as backache. Neither of these formulations is recommended for longer than a 2 to 3 week period. Carisoprodol is metabolized to meprobamate an anixolytic 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, carisoprodol (Soma®). *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) **ANTISPASTICITY/ANTISPASMODIC DRUGS:** **Tizanidine (Zanaflex®, generic available)** is a centrally acting alpha2-adrenergic agonist that is FDA approved for management of spasticity. (Malanga, 2008)) One study (conducted only in females) demonstrated a significant decrease in pain associated with subacute and 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. This medication is related to clonidine and should not be discontinued abruptly. Weaning should occur gradually, particularly in patients that have had prolonged use. (Zanaflex-FDA, 2008) **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.
Myobloc	See Botulinum toxin.
Myofascial pain	Overview of this pain syndrome (not a procedure): Myofascial pain is defined as pain or autonomic phenomena referred from active trigger points, with associated dysfunction including restricted range of motion. The trigger point is a focus of hyperirritability in a palpable taut band of skeletal muscle that, when compressed, is locally tender and, if sensitized, gives rise to referred pain and tenderness. However, trigger points may be observed in up to 33-50% of adults in a general medicine practice according to the International Association for the Study of Pain. The pain quality is dull or achy and associated with autonomic changes (abnormal sweating, lacrimation, flushing and temperature changes). Active trigger points cause pain at either rest or activity. Latent trigger points are not painful but present with other signs, primarily restricted movement and weakness. The therapy for myofascial pain requires enhancing central inhibition through pharmacology or behavioral techniques and simultaneously reducing peripheral inputs through physical therapies including exercises and trigger point-specific therapy. Long-term clinical efficacy of most treatment for trigger points and myofascial pain has not been determined due to lack of research. (Graff-Radford, 2004) (Alvarez,

	2002) (Borg-Stein, 2002
Myotherapy	See Massage therapy.
Nabilone (Cesamet®)	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.
Nabumetone (Relafen®)	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Nabumetone (Relafen®) listing for more information and references.
Naloxone (Narcan®)	Recommended in hospital-based and emergency department settings as currently indicated to address opioid overdose cases. Recommended on a case-by-case basis for outpatient, pre-hospital use, to treat opioid overdose for patients who are prescribed opioids for acute and chronic pain (malignant and non-malignant) due to documented pathology. (See Criteria Below) There is little evidence-based research to guide who should receive naloxone in an outpatient medically prescribed setting. Guidance is partially dependent on risk factors for overdose. When used in these pre-hospital settings, the patient will still require emergency and perhaps long term care. *Overview:* Naloxone (Narcan®), an opioid antagonist that has no abuse potential, is recommended for the complete or partial reversal of opioid depression (including respiratory depression) induced by natural and synthetic opioids. Drugs for which naloxone is not effective for treating in overdose situations include benzodiazepines, barbiturates, stimulants and/or alcohol. Naloxone may be helpful if opioids are taken in combination with other sedatives or stimulants. Naloxone treatment in an outpatient setting was initially used to address individuals who experienced overdose due to heroin in programs referred to as overdose education and naloxone distribution programs (OEND). These were initially developed by community-based and public health organizations to prevent opioid overdose fatalities. They have now expanded to individuals who use pharmaceutical opioids illicitly, with additional research aimed at programs to prevent pharmaceutical overdose deaths in medical practice settings. Until recently, obtaining naloxone and training in use of the drug was difficult to

	access (generally only available in Syringe Exchange Programs and from harm reduction organizations). (Frank 2015) (Mueller, 2015) (SAMHSA, 2014) (Oluwajenyo, 2014) (Doe-Simkins, 2014) *Available formulations:* (1) Naloxone 0.4 mg/ml for injection; (2) Evzio 2-Pack Auto-Injector 0.4 mg/0.4 mL solution for injection. Naloxone is approved for intravenous, intramuscular and subcutaneous administration. Off-label routes include endotracheal, sublingual, inhaled and intranasal. The product used for intranasal use is a prefilled syringe at a concentration of 2 mg/2 mL (IMS/Amphastar, prefilled syringe). The intranasal mucosal atomizer (MAD-Nasal, LMA North America) fits onto the luer-lock of the prefilled syringe or a standard syringe. Naloxone "kits" used in the naloxone distribution programs generally include 2 doses of naloxone and other items (syringes, brochures, simple rescue breathing masks, and educational materials about topics such as overdose risks). (Bailey, 2014) (Coffin, 2013) (Beletsky, 2015) Also see Evzio® (naloxone). *Education:* There is no one standard program that is suggested for education for naloxone use, although this is suggested for not only the patient, but also for family and/or friends. Components suggested include training in opioid overdose prevention, recognition, and response. Overdose response training in community programs generally involves information on how to seek help from emergency medical systems, how to perform rescue breathing, and how to administer naloxone. Staying with the victim until recovery or help arrives is emphasized. (Mueller, 2015) *Signs of overmedication and overdose:* Signs of overmedication include unusual sleepiness or drowsiness, mental confusion, slurred speech and other evidence of intoxicated behavior, slow or shallow breathing, slow heartbeat and low blood pressure. Over a period of several hours progression to overdose can occur if intervention does not occur. The victim may be unarousable at this point with evidence of extreme breathing difficulty and cyanosis. The essential finding is respiratory depression. (SAMHSA, 2014) (Boyer, 2012) *Patients at risk for overdose* The following have been outlined as risk factors for overdose. **As can be noted, some of these risk factors could be considered indicators for reconsideration of opioid treatment or possible termination as per the current ODG guideline recommendation**. Patients with many of these risk factors will generally also require extensive monitoring if opioid and other scheduled drug treatment is continued. See MTUS Opioids Medical Treatmment Guidelines for information and recommendations. (1) Patients at high risk for overdose because of a legitimate medical need for analgesia, coupled with a suspected or confirmed history of substance abuse, dependence or non-medical use of prescriptions or illicit opioids. (2) Patients taking high doses of opioids for long-term management of chronic malignant or non-malignant pain (according to the MTUS Opioid Guidelines, this value is ≥ 80 mg of oral morphine equivalents a day (MED)); (3) Patients who have received rotating opioid medication regimens (and are potentially at risk for incomplete tolerance); (4) Patients with a history of recent discharge from emergency medical care following opioid intoxication; (5) Patients who have completed opioid detoxification or have been

	abstinent for a period of time, including due to incarceration (due to possible reduced opioid tolerance and high risk of relapse to opioid use); (6) Patients who inject opioids; (7) Patients who combine opioids with other central nervous system depressants (either prescribed such as sedative hypnotics, muscle relaxants and benzodiazepines, or with alcohol, marijuana, or illicit drugs); (8) Patients with comorbid mental health disease (including depression, anxiety, and/or somatization disorder), in part as they are more likely to receive higher doses of opioids and/or concomitant sedative hypnotics; (9) Patients with comorbid central nervous system, kidney, liver or lung disease (the latter including chronic obstructive pulmonary disease, emphysema, asthma and sleep apnea or those who smoke); (10) Patients with any methadone prescription who are opioid naïve; (11) Patients enrolled in a methadone or buprenorphine detoxification and/or maintenance program; (12) Patients who live remotely from medical care. (Webster, 2011) (SAMHSA, 2014) (Brason, 2013) (Albert, 2011) (Boyer, 2012) *Adverse effects of use of naloxone (including withdrawal symptoms) with use:* Adverse effects depend on dose and route of administration, with intravenous administration and higher doses producing more events and opioid withdrawal symptoms. Adverse effects after opioid depression reversal include cardiac and cardiac related disorders (arrest, rapid heartbeat, hypertension, and ventricular dysrhythmias), gastrointestinal disorders (nausea and vomiting), central nervous system disorders (seizures and tremor), and respiratory disorders (pulmonary edema). Overt withdrawal symptoms can also be seen. Acute withdrawal generally subsides in about 2 hours. Patients should be observed for at least 2 hours after the last dose of naloxone to observe for recurrence of respiratory depression and other narcotic effects. (Wermeling, 2015) See Weaning, opioids (specific guidelines), Opioid withdrawal signs and symptoms. *Criticisms and concerns of use:* There is concern that distribution of naloxone to reverse opioid related overdoses may increase opioid use (primarily due to removing the threat of overdose) or delay entry into addiction treatment by reducing interactions with emergency healthcare providers. Other concerns include safety of allowing lay persons to administer naloxone, the possibility that the victim of overdose may return to the overdose state after a naloxone injection (due to the fact that the drug has a shorter half-life than many opioids), and possible precipitation of opioid withdrawal with use of naloxone. (Oluwajenyo, 2014) *Legal issues and fear of criminal sanctions:* There are multiple legal issues involved with the prescription of naloxone. State laws generally discourage or prohibit third-party prescribing (giving a prescription to a person other than the intended recipient) or to a person who has not been examined (prescription via standing order). These prohibitions are important as the people who are often best able to use naloxone in an overdose situation (family members or friends) will fall under these categories. Some providers are reluctant to prescribe naloxone due to liability concerns. Even where naloxone is available, the fear of legal repercussion may keep bystanders with access to naloxone from administering the drug. Another more general issue is that regardless of whether naloxone is available or not, bystanders may not summon medical aid due to fear of legal

	consequences. Laws that address these issues include those that remove the possibility of negative legal action against prescribers and lay people who administer the drug as well as implementation of "Good Samaritan" laws (described as those that allow for the summoning of emergency responders without fear of arrest or other negative legal consequences). As of December 2014, 28 jurisdictions now have laws that address access to naloxone for people at risk for opiate overdose. Twenty-two states have passed related Good Samaritan laws as of 2014. Criminal immunity is provided in 17 jurisdictions for prescribers who prescribe, dispense, or distribute naloxone to laypersons. See below for additional information on state laws on these topics. (Straus, 2013) (Beletsky, 2012) *Pilot programs that include pre-hospital, clinical medicine settings for distribution of naloxone:* Project Lazarus was established in Wilkes County, NC in 2008 to address high drug overdose deaths. The goal of this program, in part, is to provide safe access to care for patients with chronic pain. Education of clinicians providing drugs is strongly emphasized. Patients receiving drugs watch a 20-minute DVD that covers responsibilities in pain management, storage of meds, disposal of meds, recognizing and responding to an overdose and options for substance abuse treatment. Naloxone kits in this program were free. (Albert, 2011) (Brason, 2013) **Criteria for prescriptions for naloxone for patients receiving opioids for pain in clinical settings for potential pre-hospital rescue (consensus based):** (1) There should be documentation of a complete history that includes questions about prior drug and alcohol use (including previous overdose), recent results of a screening tool for potential prescription drug abuse (such as the SOAPP-R), a complete list of chronic medical illnesses, and a complete medication list. See Opioids, screening tests for risk of addiction & misuse. (2) There should be evidence that education has been provided to the patient, with encouragement that family members and/or friends participate in this. Suggested education should include information about how to administer naloxone with practice with a training device if available. Other suggested components of training should include education on opioid overdose prevention, recognition of overdose and response to the event in addition to naloxone administration. Information on how to seek help from emergency medical systems should be made available and include an emphasis on staying with the patient until help arrives. (3) There should be evidence that the patient has been counseled about drug use including risk of self-escalation of doses, and self-monitoring of function. Patients should be advised to keep meds secure and to not share them. (4) There should be evidence that the patient has been given information about the risk of overdose, including risk factors for such (see the list above). (5) It is recommended that before prescribing, clinicians become knowledgeable about their states laws in terms of third-party prescribing, prescription via standing order, and "Good Samaritan" laws. This is, in part, as family members, friends, or other members of the community may

	be involved in the use of the drug for rescue. For additional information, the following can be accessed: (a) Legal Interventions to Reduce Overdose Mortality; Naloxone Access and Overdose Good Samaritan Laws;" Available at: https://www.networkforphl.org/_asset/qz5pvn/network-naloxone-10-4.pdf. (b) Overview of State Legislation to Increase Access to Treatment for Opioid Overdose. NASADAD, 2013. Available at: http://attcnetwork.org/userfiles/file/MidAmerica/Opioid-Overdose-Policy-Brief-Final6.pdf. (6) A generic formulation is recommended as first-line treatment. Branded products such as Evzio® are only recommended if generic is not available. **Consideration for use should occur in the following situations:** (1) Patients with the following problems who require opioids for legitimate medical reasons (who generally are treated for acute pain or palliative care/malignancy in a workers' compensation setting): active abusers of scheduled drugs including opioids or those patients with a history of substance abuse; dependence or non-medical use of prescription or illicit drugs; patients recently discharged from emergency medical care following opioid intoxication; those who have been abstinent from opioids for a period due to detoxification including due to incarceration (due to possible reduced opioid tolerance and high risk of relapse to opioid use). (2) Patients on methadone or buprenorphine maintenance. (3) Patients who have had their opioids rotated (particularly to methadone) and may be at risk for incomplete tolerance. (4) The patient is prescribed high doses of opioids (≥ 80 mg MED of oral morphine equivalents according to the MTUS Opioid Guidelines) and tapering to less than this value or below is not practical or contraindicated. Particular consideration of naloxone prescribing should be given if (a) the patient is on concomitant benzodiazepines, sedative hypnotics (such as sleep aids), antidepressants, or muscle relaxants, (b) the patient has a history of pulmonary disease including chronic obstructive pulmonary disease, emphysema, asthma, and/or sleep apnea, (c) the patient has a history of liver and/or kidney disease, and/or (d) the patient has a history of mental illness. (5) The patient lives remotely from emergency care and is on high dose opioids. (6) The patient voluntarily requests naloxone. **Considerations once prescribed:** (1) Only one kit should be dispensed at any time. (2) Renewal should be by prescription based on medication expiration or damage. If the kit has been used, information should be provided as to why, and further treatment given as indicated based on this. Refer to the MTUS Opioids Treatment Guidelines for information and recommendations.

Naltrexone	Recommended as a second-line option for opioid dependence

(Vivitrol® extended-release injectable suspension)	detoxification treatment, versus methadone or buprenorphine first-line treatment. On Oct. 12, 2010, the FDA approved Vivitrol to treat and prevent relapse after patients with opioid dependence have undergone detoxification treatment. Vivitrol is an extended-release formulation of naltrexone administered by intramuscular injection once a month. Naltrexone works to block opioid receptors in the brain. It blocks the effects of drugs like morphine, heroin, alcohol, and other opioids. (FDA, 2010) A study in *The Lancet* concluded that extended-release (ER) naltrexone (Vivitrol), a receptor antagonist, is a safe and effective option for treating opioid dependence disorder (ODD). Those who received once-monthly injections of ER naltrexone had significantly more opioid-free weeks during a 6-month period and fewer cravings than those who received placebo. Methadone and buprenorphine are opioid agonists that have previously been shown to be effective for managing ODD. Naltrexone, on the other hand, is a μ-opioid receptor antagonist. It has a differentiated mechanism of action that blocks opioid receptors in the brain, producing no euphoria or sedation and generating no physical opioid dependence. Vivitrol offers an antagonist or nonaddictive, nonopioid option. The once-a-month administration helps to ensure patient compliance and that therapeutic concentrations of the medication are maintained. (Krupitsky, 2010) Continued use of once-monthly extended-release naltrexone intramuscular injection (Vivitrol) is a safe and effective method of preventing relapse to opioid dependency after detoxification. It significantly increased the number of abstinence weeks (90% vs 35% for placebo) and the likelihood of total abstinence (36% vs 23%). (Krupitsky, 2011) See also Embeda (morphine sulfate & naltrexone hydrochloride).
Naproxen (Naprosyn®, EC-Naprosyn®, Anaprox®, Anaprox DS®, Aleve® [otc], Naprelan®)	Recommended as an option. Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) for the relief of the signs and symptoms of osteoarthritis. See NSAIDS (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Naproxen (Naprosyn®, EC-Naprosyn®, Anaprox®, Anaprox DS®, Aleve® [otc], Naprelan®) listing for more information and references. See also Anti-inflammatory medications.
Narcotics	Refer to the MTUS Opioids Treatment Guidelines for information and recommendations;
Nausea	See Antiemetics (for opioid nausea).
Nerve blocks	See Intravenous regional sympathetic blocks (for RSD, nerve blocks).
Nerve conduction studies (NCS)	See Electrodiagnostic testing (EMG/NCS).
Neuroreflexotherapy	Not recommended in the U.S. until specifically trained and experienced clinicians are available.
Neurometer®	See Current perception threshold (CPT) testing.
Neuromodulation devices	See Spinal cord stimulators.
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)
Neurontin® (gabapentin)	Neurontin® is a brand name for gabapentin produced by Pfizer subsidiary Parke-Davis. See Gabapentin.
NeuroPhysiologic Pain Profile (NP3)	Not recommended. There are no published studies. A private company NeuroPAS developed the NeuroPhysiological Pain Profile, or the NP3, and is trying to market it. For other tests, see Psychological evaluations; Cytokine DNA testing; Functional imaging of brain responses to pain; CRPS, diagnostic tests; Quantitative sensory threshold (QST) testing; Current perception threshold (CPT) testing; Genetic testing for potential opioid abuse.
Nexium® (esomeprazole magnesium)	Recommended since PPIs are all approximately equivalent clinically and OTC Nexium is more accessible and economical than prescription PPIs. See Proton pump inhibitors (PPIs). The FDA has approved generic esomeprazole (FDA, 2015), and they have approved prescription to over-the-counter (OTC) switch. (FDA2, 2015)
Nonprescription medications	Recommend acetaminophen (safest); NSAIDs (aspirin, ibuprofen). (Bigos, 1999) A 2008 Cochrane review found that NSAIDs are not more effective than acetaminophen for acute low-back pain, but acetaminophen had fewer side effects, which support recommending NSAIDs as a treatment option after acetaminophen. (Roelofs-Cochrane, 2008) There should be caution about daily doses of acetaminophen and liver disease if over 3 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) See MTUS Low Back Complaints. *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 pain and mixed pain conditions such as osteoarthritis (and other nociceptive pain) in patients with neuropathic pain. (Namaka, 2004) (Gore, 2007) See NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & Medications for acute pain (analgesics). 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) The risks of NSAIDs in older patients, risks which include increased cardiovascular risk and gastrointestinal toxicity, may outweigh the benefits of these medications. (AGS, 2009)
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). A history of ulcer complications is the most important predictor of future ulcer complications associated with NSAID use. (Garcia Rodriguez, 1994) (Malfertheiner, 2009) *H. Pylori and NSAID use:* While routine screening for *H. Pylori* is not indicated in patients who are about to start NSAIDs, eradication of *H pylori* prior to initiation of therapy has been suggested to reduce subsequent risk of GI ulceration. At best, consensus guidelines indicate pre-screening for *H. Pylori* prior to starting NSAID treatment for those with GI risk factors for ulceration as listed above. Eradication of *H. pylori* alone is not sufficient to prevent ulcer bleeding in NSAID users with high gastrointestinal risk. There are no clear-cut guidelines for treatment of *H. Pylori* after initiation of NSAID treatment and this topic remains controversial. At this time, there is currently no evidence to support the routine use of a proton-pump inhibitor in a patient without the above GI risk factors for ulceration who has had a

	history of eradicated *H. Pylori* (i.e. a previous history of treated *H. Pylori* without evidence of ulceration is not an indicator for either the use of a Cox-2 NSAID or a proton-pump inhibitor). Consensus guidelines do currently indicate that patients who have a history of GI ulceration (which was determined to be secondary to *H. Pylori)* who develop breakthrough dyspepsia while treated with a proton-pump inhibitor should have the following: (1) NSAID therapy withheld; & (2) GI evaluation undertaken. (Malfertheiner, 2009) (Chan, 2001) (Fock, 2009) (Laine, 2006) (Chan, 2002) (Garcia Rodriguez, 1994) 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 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 major cardiac risk factors. It is then suggested that acetaminophen or aspirin be used for short-term needs. *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) In particular, it is suggested that in individuals at increased risk for GI bleeding (see above) a consideration be made to switch to an antidepressant with a lower degree of inhibition of serotonin reuptake (Intermediate reuptake: venlafaxine, amitriptyline, imipramine, citalopram; Low reuptake: desipramine, doxepin, trazodone, bupropion, mirtazapine). SSRIs with the highest degree of inhibition of serotonin reuptake include paroxetine, sertraline, and fluoxetine. (Looper, 2007) *Treatment of dyspepsia secondary to NSAID therapy:* Stop the NSAID, switch to a different NSAID, or consider H2-receptor antagonists or a PPI. A recent systematic review concluded that slow-release formulations of NSAIDs are associated with a greater risk of upper GI bleeding/perforation, and should be used with care. The RR of upper GI bleeding/perforation was 4.50 for traditional NSAIDs, 2.69 for ibuprofen, and 1.88 for coxibs. Estimated RRs were 5.63 for naproxen immediate release, but as much as 14.54 for some slow-release formulations. (Massó, 2010) In patients with prior myocardial infarction (MI), most NSAIDs are associated with an increased risk for death and recurrent MI, a large cohort study concludes. Use of NSAIDs was associated with a 45% increased risk for death or recurrent MI in the first 7 days of treatment and a 55% increased risk if treatment continued to 3 months. There is no apparent safe therapeutic window for NSAIDs in patients with prior MI and low-dose and short-term use of NSAIDs are not safe. All NSAIDs except naproxen were associated with an increased risk for death or recurrent MI, with diclofenac having the highest risk (RR in the first week of treatment, 3.26), an even higher cardiovascular risk than the selective COX-2 inhibitor rofecoxib, which was withdrawn from the market due to its unfavorable cardiovascular risk profile. (Schjerning, 2011) A large systematic review of available evidence on NSAIDs confirms that naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk. Rofecoxib (Vioxx) was associated with a significantly increased risk of cardiovascular events and was taken off the market, but diclofenac, a widely used NSAID, also poses an equivalent risk to patients. Indomethacin is an older, rather toxic drug, and the evidence on cardiovascular risk casts doubt on its continued clinical use. Naproxen was consistently shown to be safe, even at high doses, suggesting it should be the NSAID of choice in patients with increased cardiovascular risk. Naproxen was shown to be safer than ibuprofen, with the risk of cardiovascular events increasing with ibuprofen at daily doses ranging from 1200 mg to 1600 mg. If ibuprofen is used in high-risk patients, the dose should be kept low, but if a higher dose is needed, clinicians should switch to naproxen. Celecoxib (Celebrex), on the whole, had an increased risk of cardiovascular events at low and high doses, and should not be used in patients at high risk of cardiovascular disease. The authors commented that 10 years ago there were many NSAIDs in widespread use, but the number of drugs considered safe to use has declined substantially, down to just two, naproxen and low-dose ibuprofen. (McGettigan, 2011) There is a high prevalence of current NSAID use

	among groups at-risk for significant drug-related adverse events or who have major chronic conditions that are relative contraindications to NSAID use. (Adams, 2011) A new meta-analysis looking at the vascular and gastrointestinal effects of NSAIDs shows that the vascular risks associated with high-dose diclofenac and possibly ibuprofen are similar to the established risks associated with coxibs. High-dose naproxen, however, was associated with less vascular risk than the other NSAIDs. Further analysis suggested that these risks can be predicted for individuals. The authors found that major vascular events were increased by about one third by a coxib or diclofenac, chiefly due to an increase in major coronary events. Compared with placebo, they note, of 1000 patients allocated to a coxib or diclofenac for a year, 3 more had major vascular events, 1 of which was fatal. NSAIDs increased the risk for upper gastrointestinal complications by 2 to 4 times, although coxibs yielded the lowest risk for these complications. Long-term use of high dose NSAIDs should be reserved for those who receive considerable symptomatic benefit from the treatment and understand the risks. (Bhala, 2013)
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. *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, ankylosing spondylitis, and treatment of acute moderate pain. *Side Effects:* See NSAIDs, hypertension and renal function; & NSAIDs, GI Symptoms and Cardiovascular Risks. *Cardiovascular*: Hypertension (≤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%), gastroesophogeal reflux (≤ 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 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) See also Zorvolex (diclofenac). *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 is not indicated for the management of acute pain and should only be used as chronic maintenance therapy. *Diflunisal (Dolobid®, generic available): Dosing:* M*ild 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®: *Mild to moderate pain (acute*); 200-400mg PO every 6 to 8 hours (max 1000mg daily). *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. *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. Indocin is not commonly used any more, now that its risks are known, so it is not recommended as a first-line NSAID. *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. See also Tivorbex (indomethacin). *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); Extended-release capsules are not recommended for acute pain. *Ketorolac (Toradol®, generic available):* 10 mg. **[Boxed Warning]:** The oral form is only recommended for short-term (up to 5 days) in management of moderately severe acute pain that requires analgesia at the opioid level and only as continuation following IV or IM dosing, if necessary. This medication is not indicated for minor or chronic painful conditions. Increasing doses beyond a daily maximum dose of 40 mg will not provide better efficacy, and will increase the risk of serious side

	effects. The FDA boxed warning would relegate this drug to second-line use unless there were no safer alternatives. *Dosing: Acute pain (transition from IV or IM) for adults < 65 years of age:* 20mg PO followed by 10mg PO every 4 to 6 hours (max 40 mg/day). An oral formulation should not be given as an initial dose. (Toradol® Package Insert) The FDA has approved a nasal formulation of ketorolac (Sprix) for short-term pain management. (FDA, 2010) *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 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 (Naprelan®): 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. *Naprelan®*: 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) Naprelan® 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. Anaprox is recommended for the management of acute painful conditions because the sodium salt is more rapidly absorbed. *EC-Naprosyn*: 375 mg or 500 mg twice daily. *Extended-release Naprelan®:* Not recommended due to delay in absorption (Naprelan® Package Insert) and risk of upper GI bleeding/perforation. (Massó, 2010)

	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. *Acute Painful Shoulder (bursitis/tendinitis):* 200 mg PO twice a day. Therapy for 7-14 days is usually adequate. *Mild to moderate pain:* Off label. (Clinoril® Package Insert) *Tolmetin (Tolectin®, Tolectin DS, Tolectin 600mg, generic available): Dosing Information: Osteoarthritis (acute and 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)
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) See MTUS chapter on Low Back Complaints.
Nucynta™ (tapentadol)	See Tapentadol.
Nuedexta	Not recommended.
Number needed to treat (NNT)	Recommended as a measure of absolute risk in evaluating drug therapies. This is the average number of patients that need to be treated in order to have improvement in one patient. As an example, for every 4 patients treated with neuropathic pain, pain relief described as good is found in 1 patient. The NNT is a useful and relatively simple tool for practicing evidence-based medicine. This calculation can be applied to intervention studies and reflects the number of additional patients who need to receive an intervention to prevent 1 additional outcome. In this recent study, using NNT was superior to achieve participant consent versus other explanations. (Halvorsen, 2007)

Nuvigil	See Armodafinil (Nuvigil).
Occupational therapy (OT)	See Physical therapy.
Office visits	Recommended as determined to be medically necessary. Evaluation and management (E&M) outpatient visits to the offices of medical doctor(s) play a critical role in the proper diagnosis and return to function of an injured worker, and they should be encouraged. The need for a clinical office visit with a health care provider is individualized based upon a review of the patient concerns, signs and symptoms, clinical stability, and reasonable physician judgment. The determination is also based on what medications the patient is taking, since some medicines such as opioids, or medicines such as certain antibiotics, require close monitoring. As patient conditions are extremely varied, a set number of office visits per condition cannot be reasonably established. The determination of necessity for an office visit requires individualized case review and assessment, being ever mindful that the best patient outcomes are achieved with eventual patient independence from the health care system through self care as soon as clinically feasible. The ODG Codes for Automated Approval (CAA), designed to automate claims management decision-making, indicates the number of E&M office visits (codes 99201-99285) reflecting the typical number of E&M encounters for a diagnosis, but this is not intended to limit or cap the number of E&M encounters that are medically necessary for a particular patient. Office visits that exceed the number of office visits listed in the CAA may serve as a "flag" to payors for possible evaluation, however, payors should not automatically deny payment for these if preauthorization has not been obtained. *Note:* The high-quality medical studies required for treatment guidelines such as ODG provides guidance about specific treatments and diagnostic procedures, but not about the recommended number of E&M office visits. Studies have and are being conducted as to the value of "virtual visits" compared with inpatient visits, however the value of patient/doctor interventions has not been questioned. (Dixon, 2008) (Wallace, 2004) Further, ODG does provide guidance for therapeutic office visits not included among the E&M codes, for example Chiropractic manipulation and Physical/Occupational therapy. See also Telehealth.
Ondansetron (Zofran®)	Not recommended for nausea and vomiting secondary to chronic opioid use. See Antiemetics (for opioid nausea).
Onsolis™ (fentanyl buccal film)	Not recommended for treatment of chronic musculoskeletal pain. Refer to the MTUS Opioids Treatment Guidelines for information and recommendations on the use of opioids
Opana®	See Oxymorphone.
Opioid hyperalgesia	Opioid-induced hyperalgesia remains a controversial subject. The only well-controlled human study of reasonable size to date failed to show its existence. (Chu, 2011)
Opioid-induced constipation treatment	Recommended as indicated below. If prescribing opioids has been determined to be appropriate, then prophylactic treatment of constipation should be initiated. Opioid-induced constipation is a common adverse effect of long-term opioid use because the binding of opioids to peripheral

	opioid receptors in the gastrointestinal (GI) tract results in absorption of electrolytes, such as chloride, with a subsequent reduction in small intestinal fluid. Activation of enteric opioid receptors also results in abnormal GI motility. Constipation occurs commonly in patients receiving opioids and can be severe enough to cause discontinuation of therapy. *First-line:* When prescribing an opioid, and especially if it will be needed for more than a few days, there should be an open discussion with the patient that this medication may be constipating, and the first steps should be identified to correct this. Simple treatments include increasing physical activity, maintaining appropriate hydration by drinking enough water, and advising the patient to follow a proper diet, rich in fiber. These can reduce the chance and severity of opioid-induced constipation and constipation in general. In addition, some laxatives may help to stimulate gastric motility. Other over-the-counter medications can help loosen otherwise hard stools, add bulk, and increase water content of the stool. *Second-line:* If the first-line treatments do not work, there are other second-line options. About 20% of patients on opioids develop constipation, and some of the traditional constipation medications don't work as well with these patients, because the problem is not from the gastrointestinal tract but from the central nervous system, so treating these patients is different from treating a traditional patient with constipation. An oral formulation of methylnaltrexone (Relistor®) met the primary and key secondary end points in a study that examined its effectiveness in relieving constipation related to opioid use for noncancer-related pain. The effectiveness of oral methylnaltrexone in this study was comparable to that reported in clinical studies of subcutaneous methylnaltrexone in subjects with chronic noncancer-related pain. There was an 80% improvement in response with the 450 mg dose and a 55% improvement with 300 mg. Constipation drug lubiprostone (Amitiza®) shows efficacy and tolerability in treating opioid-induced constipation without affecting patients' analgesic response to the pain medications. Lubiprostone is a locally acting chloride channel activator that has a distinctive mechanism that counteracts the constipation associated with opioids without interfering with the opioids binding to their target receptors. (Bader, 2013) (Gras-Miralles, 2013) See also Tapentadol (Nucynta™), which has improved gastrointestinal tolerability for patients complaining of constipation, nausea, and/or vomiting.
Opioid pumps	See Implantable drug-delivery systems / Intrathecal drug-delivery systems (IDDSs).
Opioids	Refer to the MTUS Opioids Treatment Guidelines for information and recommendations.
Opioids, criteria for use	Refer to the MTUS Opioids Treatment Guidelines for information and recommendations.
Opioids, dealing with misuse &	Refer to the MTUS Opioids Treatment Guidelines for information and recommendations.

addiction (plus aberrant behaviors & abuse)	
Opioids, long-acting	MTUS Opioids Treatment Guidelines for additional information and recommendations. In September 2013 the FDA announced labeling changes to reflect that extended-release and long-acting opioids are no longer indicated for merely moderate pain. Previously, the labels for ER/LA opioid analgesics stated that they were indicated for moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The labels now will state that the drugs are indicated for the management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatments are inadequate, and the FDA will require manufacturers to perform more studies and clinical trials to further assess the known risks of misuse, abuse, addiction, overdose, and death. However, the FDA did not take action on dose and duration limits, as had been suggested by stakeholders. (FDA, 2013).
Opioids, psychological intervention	Refer to the MTUS Opioids Treatment Guidelines for additional information and recommendations. 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. (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, risk evaluation & mitigation strategy (REMS)	Refer to the MTUS Opioids Treatment Guidelines for additional information and recommendations on the use of opioids. The FDA announced a new Risk Evaluation and Mitigation Strategy (REMS) program and reports that it has already contacted the manufacturers of the extended-release and long-acting opioid medications hydromorphone, oxycodone, morphine, oxymorphine, morphone, methadone, and transdermal fentanyl, to require these manufacturers to develop and pay for programs to educate doctors on proper pain management, patient selection, and ensuring that their patients understand how to use these drugs safely. (FDA, 2011) On July 9, 2012, FDA approved a risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioid medications. (FDA, 2012) However, requiring drug companies to provide educational material to doctors on opioids, and making physician education under REMS voluntary are possible flaws in the plan. The propriety of having the pharmaceutical industry develop unbiased education for prescribers and patients is a concern. Another alternative would be to revise existing labeling to reflect the current clinical science and risk-benefit profile, and a black box warning might have more impact. In addition, a REMS for short-

	acting opioids has not been proposed despite data showing problems with these. (Nelson, 2012)
Opioids, specific drug list	Information on selected drugs are listed here. Refer to the MTUS Opioids Treatment Guidelines for additional information and recommendations. ***Hydrocodone/Ibuprofen*** *(Vicoprofen®; generic available):* 7.5mg/200mg. *Side Effects:* See opioid adverse effects and NSAIDS. Note: *Analgesic dose*: 1 tablet every 4-6 hours as needed for pain; maximum: 5 tablets/day (Product information, Abbott Laboratories). ***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 3000mg/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. ***Oxycodone/ibuprofen*** *(Combunox®; generic available): Side Effects:* See opioid adverse effects and NSAIDS. Note: Recommended for short-term use only (generally less than 7 days). 1 tablet (ibuprofen 400mg; oxycodone 5mg) every 6 hours as needed. Do not exceed 4 tablets/24 hours. Duration of therapy should not exceed 7 days. The elderly may be more sensitive to the usual adult dosage. (Clinical Pharmacology, 2008) ***Levorphanol*** *(Levo-Dromoran®; generic available):* 2mg tablets. Used for moderate to severe pain, when an opioid is appropriate for therapy. Levophornal 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) ***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:* Immediate release tablets for acute pain (moderate to severe); Opiate naive patients should begin with 10mg PO every 4 hours as needed. Opioid tolerant patients may need higher starting doses to achieve pain relief (10-30mg every 4 hours as needed). See specific product for full prescribing information. 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. ***Tramadol/Acetaminophen*** *(Ultracet®; generic available):* 37.5mg/325mg.

	Side Effects: See tramadol and acetaminophen. *Analgesic dose:* For short-term use ≤ 5 days in acute pain management. 2 tablets PO every 4 to 6 hours as needed (max 8 tablets/day). Not recommended in patients with hepatic impairment. (Product information, Ortho-McNeil 2004) ***Propoxyphene*** *[Off market in U.S.] hydrochloride (Darvon®; generic available), Propoxyphene napsylate (Darvon-N®), Propoxyphene/Apap (Darvocet-N; generic available): Side Effects:* See propoxyphene and acetaminophen. As of 2010, propoxyphene is being withdrawn from US market. Note: On 1/30/09 an FDA advisory panel narrowly voted to recommend that propoxyphene should be pulled from the market. The committee stated that the evidence of efficacy for propoxyphene was marginally better than placebo and never greater than acetaminophen. The agency had collected reports of more than 1,400 deaths in people who had taken the drug since 1957, though experts stressed the figure does not prove the drug was the cause of death in all cases, but they concluded that the drug showed little benefit and lots of risk. (FDA, 2009
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)
Oral corticosteroids	Not recommended for chronic pain. There is no data on the efficacy and safety of systemic corticosteroids in chronic pain, so given their serious adverse effects, they should be avoided. (Tarner, 2012) Multiple severe adverse effects have been associated with systemic steroid use, and this is more likely to occur after long-term use. And Medrol (methylprednisolone) tablets are not approved for pain. (FDA, 2013)
Oramorph® (morphine)	See MTUS Opioids Treatment Guidelines for additional information and recommendations.
Oxaprozin (Daypro®)	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Oxaprozin (Daypro®) listing for more information and references.
Oxazepam	Not recommended. See Benzodiazepines.
Oxcarbazepine (Trileptal®)	See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Oxcarbazepine listing.
Oxecta (oxycodone)	Recommended only for selected patients with risk of abuse that has been documented, but not recommended as a first-line medication for other patients. Oxecta is a tamper resistant dosage form of oxycodone approved by the FDA in June 2011 for the management of acute and chronic moderate to severe pain when the use of an opioid analgesic is appropriate. Drug abuse and diversion are serious concerns with the use of oxycodone products. When considering Oxecta, it is important to assess the likelihood of patient abuse, and based on that assessment chose Oxecta. If no risk of abuse is present, a generic form of oxycodone would be preferred. Oxecta is an immediate-release oxycodone medication that applies Aversion Technology, which uses commonly available pharmaceutical ingredients that, for example, cause the active ingredient

	to gel to prevent injection or to irritate nasal passages to discourage inhalation. Pfizer is licensing the technology in this product from Acura Pharmaceuticals. However, there is no quality evidence that this formulation has a reduced abuse liability compared with immediate-release oxycodone. (FDA, 2011) See MTUS Opioids Treatment Guidelines for additional information and recommendations.
Oxycodone	See MTUS Opioids Treatment Guidelines, Appendix F1, for dosing recommendations. .
OxyContin® (oxycodone)	On April 2, 2010, the FDA approved a new formulation of Oxyontin designed to discourage abuse, but according to the manufacturer, there is no evidence that the reformulation is less subject to misuse, abuse, diversion, overdose or addiction. (FDA, 2010) See MTUS Opioids Treatment Guidelines for additional information and recommendations.
Oxymorphone (Opana®)	Refer to the MTUS Opioids Treatment Guidelines , Appendix F1, for additional information and recommendations.
Pain management programs	See Chronic pain programs.
Paracetamol	See Acetaminophen (APAP).
Paroxetine	See SSRIs (selective serotonin reuptake inhibitors).
Pennsaid® (diclofenac sodium topical solution)	Not recommended as a first-line treatment. See the Diclofenac Sodium listing, where topical diclofenac is recommended for osteoarthritis after failure of an oral NSAID or contraindications to oral NSAIDs, and after considering the increased risk profile with diclofenac, including topical formulations. In studies Pennsaid was as effective as oral diclofenac, but was much better tolerated. Compared to a vehicle control topical placebo, outcomes were all statistically significant in favor of Pennsaid, with the standardized mean differences ranging from 0.30 to 0.39. (Towheed, 2006) FDA approved Pennsaid Topical Solution in 2009 for the treatment of the signs and symptoms of osteoarthritis of the knee, and the FDA requires a Risk Evaluation and Mitigation Strategy (REMS) from the manufacturer to ensure that the benefits of this drug outweigh its risks. (FDA, 2010) For more details see Topical analgesics, Non-steroidal antinflammatory agents (NSAIDs), and the diclofenac topical listing.
Pentazocine (Talwin/Talwin NX)	Not recommended for the treatment of chronic pain.
Percocet® (oxycodone & acetaminophen)	Percocet® is the brand name of an oxycodone and acetaminophen combination drug, produced by Endo Pharmaceuticals.
Percura®	Not recommended. Percura® is a medical food that is a proprietary blend of gamma-aminobutyric acid, choline bitartrate, L-arginine, L-serine, and other ingredients. See Medical foods.
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. (Ghoname-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) See also TENS and the MTUS Low Back Complaints.
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)
PGAP™	See Progressive goal attainment program (PGAP™).
Pharmaceuticals	See Medications.
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 treatment	Recommended as indicated below. Physical medicine encompasses interventions that are within the scope of various practitioners (including Physical Therapy, Occupational Therapy, Chiropractic, and MD/DO). Passive therapy (those treatment modalities that do not require energy expenditure on the part of the patient) is not indicated for addressing chronic pain in most instances; refer to the specific modality within these guidelines (e.g., massage, ultrasound) 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. Refer to the specific intervention within these guidelines (e.g., exercise.) 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 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) **ODG Physical Therapy Guidelines –** Allow for fading of treatment frequency (from up to 3 visits per week to 1 or less), plus active self-directed home PT. Also see other general guidelines that apply to all conditions under Physical Therapy in the ODG Preface. **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): 26 visits over 16 weeks **Arthritis** (ICD9 715): 9 visits over 8 weeks Post-injection treatment: 1-2 visits over 1 week Post-surgical treatment: Refer to the MTUS Postsurgical Treatment Guidelines Patients should be formally assessed after a "six-visit clinical trial" to evaluate whether PT has resulted in positive impact, no impact, or negative impact prior to continuing with or modifying the physical therapy.
Physical therapy (PT)	See Physical medicine treatment.
Physician-dispensed drugs	Physician dispensing is the process of distributing pre-packaged medications directly to patients at the point of care and is generally recommended only for the initial visit to provide patients with medications for acute injuries. According to some, the patient may prefer physician-dispensed drugs because of convenience. Physician-dispensing may create financial incentives that affect the use of compound drugs and other medications, due primarily to fee schedule ambiguities. In addition, physician-dispensed drugs typically do not go through the pharmacy benefit management companies (PBMs) but are submitted directly to the payer. Physician dispensing has been found to be associated with higher costs and more lost time than pharmacy-dispensed medications. (White, 2014).
Piriformis injections	Recommended for piriformis syndrome after a one-month physical therapy trial. Piriformis syndrome is a common cause of low back pain and

	accounts for 6-8% of patients presenting with buttock pain, which may variably be associated with sciatica, due to a compression of the sciatic nerve by the piriformis muscle (behind the hip joint).
Piroxicam (Feldene®)	Not recommended. See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Piroxicam (Feldene®) listing for more information and references, where it is indicated that pain is not listed as an FDA approved indication. In addition, according to the AHRQ Comparative Effectiveness Report on NSAIDS, piroxicam has the highest risk of upper GI bleeding (RR of 6.3 versus 1.9 for ibuprofen), the highest risk of myocardial infarction (RR of 1.25 versus 1.06 for ibuprofen), and it was also associated with Stevens-Johnson syndrome and toxic epidermal necrolysis. (Chou, 2006) And this high-quality systematic review also pointed out the high frequency of adverse events associated with piroxicam, including GI bleeding, renal failure, hypertension, and heart failure. In this study piroxicam was second only to ketorolac in its ability to induce gastrointestinal bleeding. Long-term use of full dosage piroxicam is potentially harmful in older adults due to its long half-life and long duration. (Massó, 2010) So piroxicam is not recommended as a first-line NSAID.
Polysomnography	Recommended after at least six months of an insomnia complaint (at least four nights a week), unresponsive to behavior intervention and sedative/sleep-promoting medications, and after psychiatric etiology has been excluded. Not recommended for the routine evaluation of transient insomnia, chronic insomnia, or insomnia associated with psychiatric disorders. Home portable monitor testing may be an option. A polysomnogram measures bodily functions during sleep, including brain waves, heart rate, nasal and oral breathing, sleep position, and levels of oxygen saturation. It is administered by a sleep specialist, a physician who is Board eligible or certified by the American Board of Sleep Medicine, or a pulmonologist or neurologist whose practice comprises at least 25% of sleep medicine. (Schneider-Helmert, 2003) According to page 3-17 of the AMA Guides (5th ed), sleep disorder claims must be supported by formal studies in a sleep laboratory. (Andersson, 2000) However, home portable monitor testing is increasingly being used to diagnose patients with obstructive sleep apnea (OSA) and to initiate them on continuous positive airway pressure (CPAP) treatment, and the latest evidence indicates that functional outcome and treatment adherence in patients evaluated according to a home testing algorithm is not clinically inferior to that in patients receiving standard in-laboratory polysomnography. (Kuna, 2011) Insomnia is primarily diagnosed clinically with a detailed medical, psychiatric, and sleep history. Polysomnography is indicated when a sleep-related breathing disorder or periodic limb movement disorder is suspected, initial diagnosis is uncertain, treatment fails, or precipitous arousals occur with violent or injurious behavior. However, polysomnography is not indicated for the routine evaluation of transient insomnia, chronic insomnia, or insomnia associated with psychiatric disorders. (Littner, 2003) **Criteria for Polysomnography:**

	Polysomnograms / sleep studies are recommended for the combination of indications listed below: (1) Excessive daytime somnolence; (2) Cataplexy (muscular weakness usually brought on by excitement or emotion, virtually unique to narcolepsy); (3) Morning headache (other causes have been ruled out); (4) Intellectual deterioration (sudden, without suspicion of organic dementia); (5) Personality change (not secondary to medication, cerebral mass or known psychiatric problems); (6) Sleep-related breathing disorder or periodic limb movement disorder is suspected; & (7) Insomnia complaint for at least six months (at least four nights of the week), unresponsive to behavior intervention and sedative/sleep-promoting medications and psychiatric etiology has been excluded. A sleep study for the sole complaint of snoring, without one of the above mentioned symptoms, is not recommended.
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®)	Recommended in neuropathic pain conditions and fibromyalgia, but not for acute pain. Pregabalin (Lyrica®) an anticonvulsant 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. This Cochrane review concluded that pregabalin has proven efficacy in neuropathic pain conditions and fibromyalgia. A minority of patients will have substantial benefit with pregabalin, and more will have moderate benefit. Many will have no or trivial benefit, or will discontinue because of adverse events. Individualization of treatment is needed to maximize pain relief and minimize adverse events. There is no evidence to support the use of pregabalin in acute pain scenarios. (Moore-*Cochrane*, 2009) In treating diabetic neuropathy and postherpetic neuralgia compared with placebo, pregabalin is associated with a modest increase in the number of patients experiencing meaningful pain reduction. In treating fibromyalgia, compared with placebo, pregabalin alone is associated with a small increase in the number of patients experiencing meaningful pain reduction. (Moore, 2014)
Prevacid® (lansoprazole)	See Proton pump inhibitors (PPIs).
Prialt®	See Ziconotide (Prialt®).
Prilosec® (omeprazole)	See Proton pump inhibitors (PPIs).
Progressive goal attainment program (PGAP™)	Recommended as an option where there is access to trained providers. PGAP is a standardized community-based intervention delivered by OTs, PTs, kinesiologists, nurses, rehabilitation counselors and psychologists, who have been trained by the PGAP program. The primary goal of PGAP

	is to reduce psychosocial barriers to return-to-work. PGAP has produced positive results for individuals suffering from musculoskeletal conditions, depression, cancer, and other debilitating health conditions. This study showed that participation in PGAP increased the probability of return to work following whiplash injury by more than 50%. (Sullivan, 2006) Findings suggest that PGAP can be a cost-effective means of improving function and facilitating return to work in individuals at risk for prolonged disability. (Sullivan, 2010) (Adams, 2007) **Criteria for the Progressive goal attainment program (PGAP™):** - Lack of improvement with early active physical therapy - Off work at least 5 weeks, but less than 5 months of continuous time lost - Surgery not planned or likely - No evidence of drug or alcohol problem - Not currently in work hardening - Maximum of 10 weeks treatment with one hour sessions on a weekly basis (L&I, 2013)
Prolotherapy	Not recommended. Prolotherapy describes a procedure for strengthening lax ligaments by injecting proliferating agents/sclerosing solutions directly into torn or stretched ligaments or 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) This recent Cochrane review concluded that, when used alone, prolotherapy is not an effective treatment for chronic low-back pain, but when combined with spinal manipulation, exercise, and other co-interventions, prolotherapy may improve chronic low-back pain and disability, but this statement is confounded by co-interventions and heterogeneity of studies. (Dagenais-*Cochrane*, 2007) This systematic review concluded that despite its use for over 50 years, there is no evidence of efficacy for prolotherapy injections alone for chronic low back pain. (Dagenais, 2008) According to this review, additional larger, randomized controlled trials are needed to make specific recommendations regarding prolotherapy. (Distel, 2011)
Promethazine (Phenergan®)	Not recommended for nausea and vomiting secondary to chronic opioid use. See Antiemetics (for opioid nausea).
Propoxyphene (Darvon®)	Not recommended. [Off market in U.S.]
Proton pump inhibitors (PPIs)	Recommended for patients at risk for gastrointestinal events. See NSAIDs, GI symptoms & cardiovascular risk. Prilosec® (omeprazole), Prevacid® (lansoprazole) and Nexium® (esomeprazole magnesium) are PPIs. Omeprazole provides a statistically significantly greater acid control

	than lansoprazole. (Miner, 2010) Healing doses of PPIs are more effective than all other therapies, although there is an increase in overall adverse effects compared to placebo. Nexium and Prilosec are very similar molecules. For many people, Prilosec is more affordable than Nexium. Nexium is not available in a generic (as is Prilosec). Also, Prilosec is available as an over-the-counter product (Prilosec OTC®), while Nexium is not. (Donnellan, 2010) In general, the use of a PPI should be limited to the recognized indications and used at the lowest dose for the shortest possible amount of time. PPIs are highly effective for their approved indications, including preventing gastric ulcers induced by NSAIDs. Studies suggest, however, that nearly half of all PPI prescriptions are used for unapproved indications or no indications at all. Many prescribers believe that this class of drugs is innocuous, but much information is available to demonstrate otherwise. If a PPI is used, omeprazole OTC tablets or lansoprazole 24HR OTC are recommended for an equivalent clinical efficacy and significant cost savings. Products in this drug class have demonstrated equivalent clinical efficacy and safety at comparable doses, including esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix), dexlansoprazole (Dexilant), and rabeprazole (Aciphex). (Shi, 2008) A trial of omeprazole or lansoprazole had been recommended before Nexium therapy (before it went OTC). The other PPIs, Protonix, Dexilant, and Aciphex, should be second-line. According to the latest AHRQ Comparative Effectiveness Research, all of the commercially available PPIs appeared to be similarly effective. (AHRQ, 2011)
Provigil® (modafinil)	Provigil is the brand name for modafinil, manufactured by Cephalon, and is approved by the FDA for the treatment of narcolepsy. Prescribers using Provigil for sedation effects of opiate should consider reducing the dose of opiates before adding stimulants. See Modafinil (Provigil®).
P-Stim™ (pulse stimulation treatment)	See Auricular electroacupuncture.
Psychological evaluations	Recommended based upon a clinical impression of psychological condition that impacts recovery, participation in rehabilitation, or prior to specified interventions (e.g., lumbar spine fusion, spinal cord stimulator, implantable drug-delivery systems). (Doleys, 2003) Psychological evaluations are generally accepted, well-established diagnostic procedures not only with selected use in pain problems, but also with more widespread use in subacute and 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 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 2nd ed - Battery for Health Improvement, (2) MBHI - Millon Behavioral Health Inventory [has been superseded 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) Chronic pain may harm the brain, based on using functional magnetic resonance imaging (fMRI), whereby investigators found individuals with chronic back pain (CBP) had alterations in the functional connectivity of their cortical regions - areas of the brain that are unrelated to pain - compared with healthy controls. 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) Maladjusted childhood behavior is associated with the likelihood of chronic widespread pain in adulthood. (Pang, 2010) Psychosocial factors may predict persistent pain after acute orthopedic trauma, according to a recent study. The early identification of those at risk of ongoing pain is of particular importance for injured workers and compensation systems. Significant independent predictors of pain outcomes were high levels of initial pain, external attributions of responsibility for the injury, and psychological distress. Pain-related work disability was also significantly predicted by poor recovery expectations, and pain severity was significantly predicted by being injured at work.

	(Clay, 2010) See also Comorbid psychiatric disorders.
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 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) Several recent reviews support the assertion of efficacy of cognitive-behavioural therapy (CBT) in the treatment of pain, especially chronic back pain (CBP). (Kröner-Herwig, 2009) **ODG Psychotherapy Guidelines:** - Up to 13-20 visits over 7-20 weeks (individual sessions), if progress is being made. (The provider should evaluate symptom improvement during the process, so treatment failures can be identified early and alternative treatment strategies can be pursued if appropriate.) - In cases of severe Major Depression or PTSD, up to 50 sessions if progress is being made.
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).
Qigong	See Internal qigong.
QSART	Not generally recommended as a diagnostic test for CRPS. See CRPS, diagnostic tests.
Quantitative sensory threshold (QST) testing	Not recommended. See also Current perception threshold (CPT) testing. Quantitative sensory testing (QST) has been used to assist in the diagnosis and management of a variety of conditions such as diabetic neuropathy and other neuropathies, as well as carpal tunnel syndrome and other nerve entrapment/compression disorders or damage. Because QST combines the objective physical sensory stimuli with the subjective patient response, it is psychophysical in nature and requires that its use be in patients who are alert, able to follow directions, and cooperative. Due to the subjective component of testing, psychological factors must be taken into consideration during testing and in evaluating test results, thus reducing the degree of objectivity QST can provide. QST is considered experimental or investigational, as there are no quality published studies to support any conclusions regarding the effects of this testing on health outcomes.
Quazepam	Not recommended. See Benzodiazepines.
Qutenza (capsaicin) 8% patch	See Capsaicin, where it is recommended only in patients who have not responded or are intolerant to other treatments. On November 17, 2009, the FDA approved an 8% capsaicin dermal patch (Qutenza, made by Lohmann Therapie-Systems AD, marketed by NeurogesX, Inc) for the management of pain associated with postherpatic neuralgia. Blood pressure should be carefully monitored for 1 hour after each application, and caution is advised when treating patients with unstable or poorly controlled hypertension or a recent history of cardiovascular or cerebrovascular events. (FDA, 2009)
Regional sympathetic blocks	See CRPS, sympathetic blocks (therapeutic).
Repackaged drugs	Repackaged drugs are prescription or over-the-counter drugs taken from initial drug producers and repackaged and repriced, usually for physician dispensing. Repackaged medications are difficult to price consistently, since a pharmaceutical product is removed from the original container with an original NDC and put into a new container with new quantities, therefore requiring a new NDC, with a new repackaging company label and price for the medication. There are no high-quality medical studies to evaluate physician dispensing of repackaged drugs versus pharmacy dispensing on patient outcomes so this is not addressed in ODG See also Compound drugs; Co-pack drugs; Medical foods; Physician-dispensed

	drugs.
Restless legs syndrome (RLS)	See specific body-part chapters in the MTUS.
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).
Roxicodone® (oxycodone)	See MTUS Guideline for the Use of Opioids to Treat Work-Related Injuries for additional information on oxycodone.
RS-4i sequential stimulator	See Interferential current stimulation (ICS).
RSD (reflex sympathetic dystrophy)	Definition of this pain syndrome (not a procedure): New name for Reflex sympathetic dystrophy (RSD) is CRPS I. See CRPS, diagnostic criteria.
Ryzolt (tramadol ER)	See MTUS Opioids Treatment Guidelines for prescribing information on opioids. The FDA has determined that Ryzolt is equivalent to generic extended release tramadol. (FDA, 2012) On 12/30/08 the FDA approved an extended-release once-daily formulation of tramadol (Ryzolt) for the management of moderate to moderately severe chronic pain. Labopharm and marketing partner in the United States, Purdue Pharma, launched the product in 100-mg, 200-mg, and 300-mg dosage strengths in the second quarter of 2009. (FDA, 2008) If a patient is already stabilized on a long-acting tramadol, then the immediate-release component of the biphasic product has the potential to cause a higher than desired blood level of tramadol, which might impact a patient in a negative way, but this has not been proven in studies. The clinical rationale for using a long-acting opioid is to maintain a stable blood level around-the-clock, so it is not entirely clear how a biphasic formulation adds to chronic, around-the-clock opioid therapy. (FDA2, 2012) In addition, efficacy was demonstrated in only one of four studies that were conducted for approval of biphasic tramadol ER. (FDA3, 2012) See also ConZip (tramadol ER), another biphasic tramadol ER that is not available as a generic.
Salicylate topicals	Recommended as an option. Topical salicylate (e.g., Ben-Gay, methyl salicylate) is significantly better than placebo in acute and chronic pain, but especially acute pain. Three double blind placebo controlled trials had information on 182 patients with acute conditions. Topical salicylate was significantly better than placebo (relative benefit 3.6; number needed to treat 2.1). Six double blind placebo controlled trials had information on 429 patients with chronic conditions. Topical salicylate was significantly better

	than placebo overall (relative benefit 1.5; number needed to treat 5.3), but larger, more valid studies were without significant effect. (Mason-BMJ, 2004) This review found evidence that was limited by the quality, validity and size of the available studies, particularly for studies in acute pain conditions like strains and sprains, where there was inadequate information to support the use of topical rubefacients containing salicylates. In chronic pain conditions such as osteoarthritis the evidence was more robust, but rubefacients appear to provide useful levels of pain relief in one in six individuals over and above those who also responded to placebo. This compares poorly with topical NSAIDs where substantial amounts of good quality evidence indicate that one in every three individuals treated will experience useful levels of pain relief over and above those who also responded to placebo. (Matthews-*Cochrane*, 2009) Neither salicylates nor capsaicin have shown significant efficacy in the treatment of OA. (Altman, 2009) Topical OTC pain relievers that contain menthol, methyl salicylate, or capsaicin, may in rare instances cause serious burns, a new alert from the FDA warns. (FDA, 2012) See also Topical analgesics; & also Topical analgesics, compounded.
Savella	See Milnacipran (Savella®).
Sclerotherapy (prolotherapy)	Not recommended for treatment of chronic pain. Sclerotherapy/prolotherapy has no proven value via well-controlled, double blind studies and may have harmful effects. (ChronicPain, 1998) See Prolotherapy.
Scrambler therapy (Calmare®)	Not recommended for the treatment of chronic pain. There are promising pilot studies, but higher quality studies are needed and are currently being conducted. The evidence is not yet sufficient to permit conclusions about the benefits of Scrambler therapy, also known as transcutaneous electrical modulation pain reprocessing, for the treatment of chronic pain. The device is intended to scramble pain information with no-pain information, to reduce the perception of pain intensity. Scrambler therapy interrupts transmission of pain signals by delivering electrical stimulation that is interpreted by the nervous system as no pain, and it is performed using a type of transcutaneous electrical stimulation (TENS) device that is specifically designed for this therapy. Cutaneous nerves are stimulated using 5 surface electrode pairs that are placed in the dermatomes above and below the pain area. Unlike conventional TENS, scrambler therapy is administered in the office setting under physician supervision. Treatment applications are interactive between the patient and the provider, with the provider attending and making adjustments approximately every 10 minutes throughout the treatment session, which typically lasts an hour. There have been pilot studies, but the preliminary findings from these pilot studies need to be validated by well-designed studies. While preliminary results suggested that cutaneous electro-stimulation with the Calmare can be hypothesized as part of a multi-modality approach to the treatment of chronic pain, further studies on larger numbers of patients are needed to assess its efficacy, to quantify the effects of inter-operator variability, and to compare results obtained from the active device versus those from a sham machine. The pilot studies are useful in informing hypothesis formation, but they do not permit conclusions on efficacy and safety due to

	small size, lack of a sham control group, and short-term follow-up period. (Marineo, 2012) (Ricci, 2012)
SDET	See Work conditioning, work hardening. The SDET (single-discipline exercise therapy) terminology is frequently used to refer to work hardening.
Sedative hypnotics	See Insomnia treatment.
Sensory nerve conduction threshold (sNCT) device	See Current perception threshold (CPT) testing.
Sentra PM™	Not recommended for the treatment of chronic pain. Sentra PM™ is a medical food that is a proprietary blend of choline bitartrate, glutamate, and 5-hydroxytryptophan. See Medical foods.
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.
Sertraline	See SSRIs (selective serotonin reuptake inhibitors).
Skelaxin® (metaxalone)	Skelaxin® is a brand name for metaxalone marketed by King Pharmaceuticals. See Metaxalone (Skelaxin®).
Sleep studies	See Polysomnography.
Sleeping pills	See Insomnia medications.
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®).
Sodium oxybate (Xyrem)	Not recommended for fibromyalgia. The FDA rejected sodium oxybate (Xyrem) for the treatment of fibromyalgia. There is substantial risk of abuse because the drug is the same as GHB (gamma-Hydroxybutyric acid), the "date-rape" drug. Currently, the drug is approved for the treatment of excessive daytime sleepiness and cataplexy associated with narcolepsy. The FDA said there was lack of convincing evidence that the risks involved in releasing the drug to a large population were balanced by its effectiveness in treating fibromyalgia-related pain and sleeping problems, because there is no data to show that it is better than existing medications. (FDA, 2014)
Soma® (carisoprodol)	See Carisoprodol (Soma®).
SpeedGel RX	Not recommended. There are no quality published studies. SpeedGel RX is a homeopathic topical analgesic gel for pain. The exact pharmacology by which SpeedGel RX works to control aches and pains associated with arthritis or trauma is unknown. According to the FDA, there is no scientific evidence to support this treatment. (NIH, 2014)
Spinal cord stimulators (SCS)	Recommended only for selected patients for specific conditions and in cases when less invasive procedures have failed or are contraindicated (see blue box below for criteria to be met when considering use of a spinal cord stimulator). Spinal cord stimulators (SCS) are indicated for selected

	patients with Complex Regional Pain Syndrome (CRPS) Type I. For use in failed back surgery syndrome (FBSS), see the MTUS Low Back Complaints. 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 Complete list of SCS References This supporting 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. (Sundaraj, 2005) 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) 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) As batteries for both rechargeable and nonrechargeable systems are nearing end of life, there are both early replacement indicators and end of service notifications. Typical life may be 8-9 years for rechargeable batteries, but this depends on the unit. In addition, the physician programmer can be used to interrogate the implanted device and determine the estimated remaining battery life. (Restore, 2011) **Indications for stimulator implantation:** • Complex Regional Pain Syndrome (CRPS) when all of the following are present: (1) there has been limited response to non-interventional care; (2) psychological clearance indicates realistic expectations and clearance for the procedure; (3) there is no current evidence of substance abuse issues; (4) there are no contraindications to a trial; (5) Permanent placement requires evidence of 50% pain relief and medication reduction or functional improvement after temporary trial. • For use in failed back surgery syndrome (FBSS), see MTUS Low Back Complaints. For average hospital LOS if criteria are met, see Hospital length of stay (LOS).
Spinal cord	• See Psychological evaluations, SCS (spinal cord stimulators).

stimulators, psychological evaluations	
Sprix (ketorolac tromethamine nasal Spray)	See Ketorolac. In May 2010, FDA approved an intranasal formulation of ketorolac tromethamine (Sprix Nasal Spray) for the short-term management of moderate to moderately severe pain requiring analgesia at the opioid level. The total duration of use of this intranasal formulation, as with other ketorolac formulations, should be for the shortest duration possible and not exceed 5 days. Both studies used for approval were for short-term pain after abdominal surgery, so it is not recommended as a first-line medication for chronic pain. (FDA, 2010)
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. SSRIs that are commonly prescribed include the following: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, & sertraline. (Clinical Pharmacology, 2010)
Stellate ganglion block	See CRPS, sympathetic blocks (therapeutic).
Stress infrared telethermography	See Thermography.
Suboxone® (buprenorphine)	See Buprenorphine.
Sudomotor axon reflex test	Not generally recommended as a diagnostic test for CRPS. See CRPS, diagnostic tests.
Sulindac (Clinoril®)	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Sulindac (Clinoril®) listing for more information and references.
Surgery	Refer to the relevant Clinical Topics section of the MTUS for recommendations. See also CRPS, sympathectomy; CRPS, spinal cord stimulators (SCS); Implantable drug-delivery systems (IDDSs); Spinal cord stimulators (SCS).
Sympathectomy	See CRPS, sympathectomy.
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 State, 2002) (BlueCross BlueShield, 2005) (Aetna, 2005) See also Interferential therapy and relevant MTUS body chapters.
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 sympathetically maintained pain conditions. (Stanton-Hicks, 2004) See CRPS, diagnostic criteria; CRPS, medications; CRPS, sympathetic and epidural blocks; & Regional sympathetic blocks.
Tai Chi	Recommended as an exercise-therapy option for arthritis, and for fibromyalgia when requested by highly motivated patients. Exercise therapy such as strengthening, stretching and aerobic programs, have been shown to be effective for arthritic pain. Tai Chi is a form of exercise that is regularly practiced in China to improve overall health and well-being. It is usually preformed in a group but is also practiced individually at one's leisure. The fact that Tai Chi is inexpensive, convenient, and enjoyable and conveys other psychological and social benefits supports the use this type of intervention for pain conditions such as arthritis. It is important to note that the results reported in this systematic review are indicative of the effect of Tai Chi versus minimal intervention (usual health care or health education) or wait list control, but establishing the specific effects of Tai Chi would require a placebo-controlled trial, which has not yet been undertaken. (Hall, 2009) Tai chi may be a helpful intervention for patients with fibromyalgia. (Wang, 2010) Outcomes from this therapy are very dependent on the highly motivated patient. See Physical medicine treatment for recommended number of visits if exercise training is prescribed.
Talwin	See Pentazocine (Talwin/Talwin NX).
Tapentadol (Nucynta™)	See MTUS Opioids Treatment Guidelines for prescribing information on opioids. Three large RCTs concluded that tapentadol was efficacious and provided efficacy that was similar to oxycodone for the management of

	chronic osteoarthritis knee and low back pain, with a superior gastrointestinal tolerability profile and fewer treatment discontinuations. (Afilalo, 2010) (Buynak, 2010) (Lange, 2010) Tapentadol is a centrally acting oral analgesic. It has two mechanisms of action, combining mu-opioid receptor agonism and norepinephrine reuptake inhibition. (Johnson, 2008) Nucynta™ (tapentadol) was made a Schedule II controlled substance. Nucynta™ may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death. (FDA, 2009) Nucynta has the same pain-relieving benefits of OxyIR, as well as the same risks that come with any opioid, but shows a significant improvement in gastrointestinal tolerability compared with oxycodone; if patients on OxyIR complain of constipation, nausea, and/or vomiting, Nucynta may be considered as a second-line choice. (Daniels, 2009) (Daniels2, 2009) (Hale, 2009) (Hartrick, 2009) (Stegmann, 2008) In one study, gastrointestinal adverse events led to discontinuation in 9% of the tapentadol group versus 22% of the oxycodone group. (Wild, 2010)
Telehealth	Recommended as an option, especially in geographically dispersed urban areas and rural areas. Current literature supports the use of telehealth in the treatment and education of patients with chronic pain. Meta-analysis shows an overall benefit of telehealth interventions over control conditions and equivalence with in-person intervention. Centralized telecare management coupled with automated symptom monitoring can result in improved pain and depression outcomes. Telecare collaborative management can increase the proportion of primary care patients with improved chronic musculoskeletal pain. Telemedicine is also cost-effective. Telehealth includes patient education, remote patient monitoring, triage, and follow-up visits and consults. Telehealth is not necessarily in lieu of traditional in clinic visits, but augments the physician patient interaction by allowing communication and monitoring outside of the clinic visit. Providers can increase contact with the patient prior to untoward events. They may also educate the patient regarding their condition, nutrition, exercise, and medication adherence. (McGeary, 2013) (Kroenke, 2010) (Kroenke, 2014) (Pronovost, 2009) See also Office visits.
Telomerase activators (TA-65)	Appropriate only in a research setting until higher quality studies are available. Telomeres are the ends protecting each chromosome that become progressively shorter each time the cell divides until the cell can no longer divide, potentially resulting various conditions associated with old age, including pain, cancer, etc. Telomerase is an enzyme used as a template when it elongates telomeres, which are shortened after each replication cycle. Chronic pain/high stress groups have significantly shorter telomere length. (Sibille, 2012) Most human cells lack sufficient telomerase to maintain telomeres, hence these genetic elements shorten with time and stress, contributing to aging and disease. A natural product-derived telomerase activator can moderately activate telomerase. (Harley, 2011) Shortening of leukocyte telomeres, the extreme ends of chromosomal DNA, is associated with risks for mortality, and may be a marker of biological aging, according to this study. (Honig, 2012)
Temazepam	Not recommended. See Benzodiazepines.

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, including reductions in medication use, 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) *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) Refer to the relevant Clinical Topics section of the MTUS for additional recommendations. *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) TENS should be differentiated from other types of electrical stimulators. See Electrical stimulators (E-stim) for a list of alternatives. *Recent studies:* A meta-analysis concluded 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. High frequency 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) A recent meta-analysis concluded that the evidence from the small number of placebo-controlled trials does not support the use of TENS in the routine management of chronic LBP. There was conflicting evidence about whether TENS was beneficial in reducing back pain intensity and consistent evidence that it did not improve back-specific functional status. There was moderate evidence that work status and the use of medical services did not change with treatment. Patients treated with acupuncture-like TENS responded similarly to those treated with conventional TENS. (Khadilkar-*Cochrane*, 2008) An evidence-based review concluded that TENS is not recommended for use in treating chronic low-back pain (level A, 2 class 1 studies) but adds that TENS should be considered to treat diabetic neuropathy (level B, 2 class 2 studies). In the highest-quality studies of chronic low back pain, there was no benefit of TENS compared to sham or placebo TENS. In diabetic polyneuropathy, some studies showed slight benefit. The authors also point out that TENS has had a long-standing role in pain management, is easy to handle, has a favorable benefit-to-risk ratio, and can be discontinued easily if it is not efficacious. (Dubinsky, 2010)
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 documented upon request. Rental would be preferred over purchase during this 30-day period.
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 opioids 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 in patients taking oral opioids than in patients receiving intrathecal opioids, and this difference seems to be related to differences in absorption. Hypogonadism secondary to opioids appears to be central, although the exact mechanism has not been determined. (Abs, 2000) (Roberts, 2002) (Roberts, 2000) The odds of being hypogonadal on long-acting opioids may be 4-5 times higher than the odds on a short-acting equipotent dose. (Rubinstein, 2012) 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) *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 (tetrahydro-cannabinol)	See Cannabinoids.
Theramine®	Not recommended for the treatment of chronic pain. See Medical foods.

Thermography (infrared stress thermography)	Not recommended. There is insufficient evidence to support the routine use of thermography for diagnosis of CRPS. Thermography is a non-invasive imaging technique, which is intended to measure temperature distribution of various organs and tissues. The infrared radiation from the tissue reveals temperature variations by producing brightly colored patterns on a liquid crystal display. Interpretation of the color patterns is claimed by some to assist in the diagnosis of many disorders such as breast cancer, Reynaud's phenomenon, digital artery vasospasm in hand-arm vibration syndrome, impaired spermatogenesis in infertile men, degree of burns, deep vein thrombosis, gastric cancer, tear-film layer stability in dry-eye syndrome, Frey's syndrome, headaches, low-back pain, reflex sympathetic dystrophy, and vertebral subluxation. There is insufficient evidence in the peer-reviewed published literature to reach conclusions concerning the effects of thermography on health outcomes for any indication. (Krumova, 2008) (Schurmann, 2007) (Gradl, 2003) See CRPS, diagnostic tests.
Thiamine (vitamin B1)	See Vitamin B.
Tiagabine (Gabitril®)	See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Tiagabine listing.
Tivorbex (indomethacin)	Not recommended except as a second-line option, because indomethacin products are not recommended as first-line choices due to potential increased adverse effects. See Indomethacin (Indocin®, Indocin SR®). In 2014 FDA approved indomethacin capsules (Tivorbex, Iroko Pharmaceuticals LLC) at 20-mg and 40-mg doses for the treatment of mild to moderate acute pain in adults. These dosages are only 20% lower in strength than the 25-mg and 50-mg indomethacin products already on the market. Tivorbex is Iroko's second approved lower-dose NSAID, since the FDA also approved diclofenac capsules (Zorvolex). While indomethacin has potent anti-inflammatory and analgesic properties, research has linked this drug to sometimes serious adverse outcomes, including cardiovascular thrombotic events, myocardial infarction, stroke, gastrointestinal ulcers, gastrointestinal bleeding, and renal events (such as acute renal failure). (FDA, 2014) According to the manufacturer, Tivorbex dissolves faster in the body compared to the currently available indomethacin immediate-release capsules, allowing for the same efficacy to be achieved with a lower overall dose of the drug. However, compared to current products, taking Tivorbex with food lowers the peak drug concentration significantly (46%) which may reduce the proposed equivalent efficacy, there are no FDA approved indications for gouty arthritis, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute painful shoulder like other NSAIDs, cost is expected to be considerably higher compared to the generically available NSAIDs, and it is not available as a suspension or extended-release formulation. It is an expensive, brand name only, second-line medication with little to no place in the treatment of workers compensation injuries. (Clinical Pharmacology, 2014)
Tizanidine (Zanaflex®)	Tizanidine is a muscle relaxant. See Muscle relaxants. See also specific Tizanidine listing.

Tolmetin (Tolectin®, Tolectin DS)	See NSAIDs (non-steroidal anti-inflammatory drugs); NSAIDs, GI symptoms & cardiovascular risk; NSAIDs, hypertension and renal function; & NSAIDs, specific drug list & adverse effects for general guidelines, as well as specific Tolmetin (Tolectin®, Tolectin DS) listing for more information and references.
Topamax® (topiramate)	See Topiramate.
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, α-adrenergic receptor agonist, adenosine, cannabinoids, cholinergic receptor agonists, γ 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 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. For example, see Duragesic® (fentanyl transdermal system).] ***Non-steroidal anti-inflammatory agents (NSAIDs):*** Recommended for the following indications: *Acute pain:* Recommended for short-term use (one to two weeks), particularly for soft tissue injuries such as sprain/strains. According to a recent review, topical NSAIDs can provide good levels of pain relief for sprains, strains, and overuse injuries, with the advantage of limited risk of systemic adverse effects as compared to those produced by oral NSAIDs. They are considered particularly useful for individuals unable to tolerate oral administration, or for whom it is contraindicated. There appears to be little difference in analgesic efficacy between topical diclofenac, ibuprofen, ketoprofen and piroxicam, but indomethacin is less effective, and benzydamine is no better than placebo. The number needed to treat for clinical success, defined as 50% pain relief, for all topical NSAIDs combined vs. placebo was 4.5 (95% confidence interval [CI], 3.9 - 5.3) for treatment periods of 6 to 14 days. Current studies indicate 6 or 7 out of 10 patients have effective pain control with topical agents vs. 4 out of 10 with placebo. The reason for the high placebo rate is that most sprain/strain injuries improve on their own. (Massey, 2010) (Mason, 2004) *Osteoarthritis and tendinitis, in particular, that of the knee, elbow, and hand or other joints that are amenable to topical treatment:* Recommended

	for short-term use (4-12 weeks). (Underwood, 2008) (Mason, 2004) (Biswal, 2006) (Green, 2002) (Niethard, 2005) (Conaghan, 2008) (Altman, 2009) (Wenham, 2010) (Zhang, 2007) (NICE, 2008) (Zhang, 2010) (Altman, 2011) The American Academy of Orthopedic Surgeons recommends topical NSAIDs if there is increased GI risk with use of NSAIDs as one option for treatment. (Richmond, 2010) There are no studies evaluating topical ketoprofen for treatment of hand osteoarthritis. Topical ketoprofen gel has been compared to oral celecoxib, with WOMAC physical function scores significant for the later but not the topical treatment. (Rother, 2007) *Osteoarthritis of the hip and shoulder:* There is little evidence to utilize topical NSAIDs for treatment of osteoarthritis of the hip or shoulder. *Osteoarthritis of the low back:* There is no evidence to recommend a NSAID dosage form other than an oral formulation for low back pain. (Roelofs, 2008) (Haroutiunian, 2010) *Widespread musculoskeletal pain:* Not recommended. *Neuropathic pain:* Not recommended as there is no evidence to support use. (Haroutiunian, 2010) (Finnerup, 2005) *General information:* The theory behind using a topical NSAID is to achieve a therapeutic concentration in the tissue adjacent to the application, allowing for safe serum concentration. This would allow for less adverse GI events, eliminate first-pass metabolism and reduce risk of other GI events associated with higher systemic doses provided with oral formulations. Overall, a high concentration of drug is observed in the dermis and muscles (equivalent to that obtained orally), with less gastrointestinal effect. Plasma concentrations are 5% to 15% of those achieved systemically. (Kienzler, 2010) Topically applied NSAIDs appear to reach the synovial fluid of joints, although the mechanism for delivery remains unclear. 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. The effect appeared to diminish over time and it was stated that further research is 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. In terms of acute pain, topical NSAIDs were found to produce a 50% reduction in pain at one week, with the most significant results obtained with use of ketoprofen, while indomethacin was barely distinguished from placebo. (Mason, 2004) *Pharmacokinetics and systemic availability:* Absorption and penetration through the skin depends on the active medication, formulation (i.e. gel vs. solution), carrier-medicated transport, and penetration enhancement. Each of these differences produces differences in systemic levels attained. The carrier may also contribute to toxicity. Toxicity by dose has not been established (especially for trials that allowed for more than one joint to be treated). Excessive amounts of topical NSAID may produce higher than

	desired levels, hindering the advantage of a topical formulation. (Haroutiunian, 2010) (Kienzler, 2010) *Compounded formulations:* There is little research available in terms of bioavailability and objective clinical endpoints for these agents. (Haroutiunian, 2010) *FDA-approved agents:* At this time, the only available FDA-approved topical NSAID is diclofenac. *Voltaren® Gel 1% (diclofenac)*: Indicated for relief of osteoarthritis pain in a joint that lends itself 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) Clinical trial data suggest that diclofenac sodium gel (the first topical NSAID approved in the US) provides clinically meaningful analgesia in OA patients with a low incidence of systemic adverse events. (Altman, 2009) The labeling for topical diclofenac has been updated to warn about drug-induced hepatotoxicity. (FDA, 2009) Voltaren Gel was effective in adults regardless of age. Treatment-related application site dermatitis was more common with Voltaren Gel, but gastrointestinal AEs were infrequent. It is recommended for osteoarthritis after failure of an oral NSAID, or contraindications to oral NSAIDs, or for patients who cannot swallow solid oral dosage forms. (Baraf, 2011) (Kienzler, 2010) See also Voltaren® Gel separate listing, where it is not recommended as a first-line treatment. *Pennsaid® (diclofenac topical solution 1.5% containing 45.5% dimithyl sulfoxide):* FDA-approved for osteoarthritis of the knee. A recent study on adverse effects of this agent compared to oral diclofenac found that the latter formulation had significantly higher events. Gastrointestinal AEs orally were 39% vs. 25.4% topically (P< 0.0001). Cardiovascular events were 3.5% orally vs. 1.5% topically (P=0.055). Liver function tests were increased more commonly in those taking oral agents. The most common adverse effect was application-site reaction. Dry skin is thought to result from the DSMO component. Long-term studies were recommended. (Roth, 2011) The dose is 40 drops to the knee four times a day. See also Pennsaid® (diclofenac sodium topical solution) separate listing, where it is not recommended as a first-line treatment. *Flector® Patch (diclofenac epolamine topical patch 1.3%):* Indicated for acute strains, sprains, and contusions. Apply one patch twice daily to most painful area. See also Flector® patch (diclofenac epolamine) separate listing, where it is not recommended as a first-line treatment. *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 and photosensitization reactions. (Diaz, 2006) (Noize, 2010) (Hindsen, 2006) (Devleeschouwer, 2008) (Matthieu, 2004) (Barbaud, 2009) Due to the high incidence of these reactions the French government removed this topical drug from the market in December 2009. This was subsequently overturned, with recommendations made to make the topical formulation available by prescription only, and by strengthening warnings as to adverse effects. (Lechat, 2010) 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) *Clinical trials:* Numerous clinical trials are ongoing, including a phase III trial for a ketoprofen patch for treatment of soft tissue injury, acute sprain/strain, and non articular rheumatism, tendinitis and bursitis, a phase III trial for ketoprofen 10% cream for treatment of acute soft tissue injury, and a topical ketoprofen gel for muscle soreness. Clinical trials show similar results between Diclofenac gel and a ketoprofen patch formulation. (Esparza, 2007) See also Ketoprofen, topical separate listing, where it is not recommended in the U.S., as there are currently no FDA-approved versions of this product, but it is a first-line drug in Europe. *Piroxicam*: There is no FDA-approved topical piroxicam agent. This drug also is known to produce drug-induced photosensitivity. (Drucker, 2011) (Barbaud, 2009) Numerous adverse effects are noted with systemic delivery of piroxicam including elevated hepatic enzymes in 1-10% in patients who receive the drug. *Adverse effects of topical NSAIDs in general:* Topical NSAIDs have a high safety margin with fewer severe gastrointestinal adverse effects. Adverse drug events occur on average in about 12% of individuals, with 75% of these including rash and/or pruritus at the application site. A recent systematic review of use of topical NSAIDs in older adults found the withdrawal rates from topical agents to be similar to that of oral NSAIDs. Gastrointestinal complaints and headaches were reported most frequently in both topical and oral NSAID groups. Anemia, liver function tests, renal abnormalities, and severe gastrointestinal events were higher in oral NSAID users. Examination of drug-related effects, including vehicles used and total dose is needed. (Makris, 2010) The use of oral NSAIDs concomitantly with topical agents is not recommended. (Peterson, 2011) See also NSAIDs, GI symptoms and cardiovascular risk; & NSAIDs, hypertension and renal function. *Cost effectiveness:* Current FDA-approved topical agents are approximately six to ten times more expensive than oral over-the-counter preparations. Savings may occur due to lack of serious adverse GI effects, and the lack of necessity of taking an ulcer-protection medication. ***Lidocaine:*** Recommended for a trial if there is evidence of localized pain that is consistent with a neuropathic etiology. See Criteria for use below. Topical lidocaine, in the formulation of a dermal patch (Lidoderm®) 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. 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. *Indications:* Recommended for localized pain that is consistent with a neuropathic etiology 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 patches are generally not recommended for non-neuropathic pain (including osteoarthritis or myofascial pain/trigger points). See Criteria for use below. Most studies have utilized the Neuropathic Pain Scale (NPS) as measure of neuropathy when there are questions of whether this is the cause of pain. There is limited information as to long-term efficacy and continued information as to outcomes should be provided to allow for on-going use. (Argoff, 2004) (Galer, 2004) (Argoff, 2006) (Dworkin, 2007) (Khaliq-*Cochrane*, 2007) (Knotkova, 2007) (Lexi-Comp, 2008) (Fishbain, 2006) (Affaitati, 2009) (Burch, 2004) (Gimbel, 2005) (Dworkin, 2003) (Finnerup, 2005) (O'Connor, 2009) Discussion about specific details of these studies are given in detail with references. Trigger points & myofascial pain: Not recommended. (Affaitati, 2009) (Dalpaiz, 2004) Refer to the relevant Clinical Topics chapter of the MTUS for additional recommendations. The FDA has approved a lidocaine/ tetracaine cream (Pliaglis®) for local analgesia. This is only indicated for superficial aesthetic procedures, such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal. (FDA, 2013) **Criteria for use of Lidoderm patches:** (a) Recommended for a trial if there is evidence of localized pain that is consistent with a neuropathic etiology. (b) There should be evidence of a trial of first-line neuropathy medications (tri-cyclic or SNRI anti-depressants or an AED such as gabapentin or Lyrica). (c) This medication is not generally recommended for treatment of osteoarthritis or treatment of myofascial pain/trigger points. (d) An attempt to determine a neuropathic component of pain should be made if the plan is to apply this medication to areas of pain that are generally secondary to non-neuropathic mechanisms (such as the knee or isolated axial low back pain). One recognized method of testing is the use of the Neuropathic Pain Scale. (e) The area for treatment should be designated as well as number of planned patches and duration for use (number of hours per day). (f) A Trial of patch treatment is recommended for a short-term period (no more than four weeks). (g) It is generally recommended that no other medication changes be made during the trial period. (h) Outcomes should be reported at the end of the trial including improvements in pain and function, and decrease in the use of other medications. If improvements cannot be determined, the medication should be discontinued. (i) Continued outcomes should be intermittently measured and if improvement does not continue, lidocaine patches should be discontinued.

	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 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) Neither salicylates nor capsaicin have shown significant efficacy in the treatment of OA. (Altman, 2009) 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:*** Not recommended except 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 Salicylate topicals; & Glucosamine (and Chondroitin Sulfate).
Topical analgesics, compounded	See Topical analgesics, where it is explained that any compounded product that contains at least one drug (or drug class) that is not recommended is not recommended. The use of compounded agents requires knowledge of the specific analgesic effect of each agent and how it will be useful for the specific therapeutic goal required.
Topical NSAIDs	See Non-steroidal antinflammatory agents (NSAIDs) entry under Topical analgesics.
Topiramate (Topamax®)	See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Topiramate listing.
Toradol	See Ketorolac (Toradol®).
Tramadol (Ultram®)	See MTUS Opioids Treatment Guidelines for general recommendations on the use of opioids. Tramadol is a centrally acting synthetic opioid analgesic and it provides inferior analgesia compared to a combination of

	Hydrocodone/ acetaminophen. (Turturro, 1998) As of November 2013, Tramadol has been designated a Schedule IV controlled substance. (DEA, 2013) Tramadol has unreliable analgesic activity and potential side effects such as serotonin syndrome. (Ray, 2013)
Tramadol/Acetamin-ophen (Ultracet®)	See specific Tramadol/Acetaminophen (Ultracet®) listing for more information and references.
Transcutaneous electrical nerve stimulation (TENS)	See TENS, chronic pain (transcutaneous electrical nerve stimulation); & TENS, post operative pain (transcutaneous electrical nerve stimulation).
Transcutaneous electrotherapy	See Electroceutical therapy (bioelectric nerve block); Galvanic stimulation; H-wave stimulation (devices); Interferential current stimulation (ICS); Microcurrent electrical stimulation (MENS devices); RS-4i sequential stimulator; Sympathetic therapy; TENS, chronic pain (transcutaneous electrical nerve stimulation); & TENS, post operative pain (transcutaneous electrical nerve stimulation).
Treatment for CRPS	See CRPS, treatment.
Trepadone™	Trepadone™ is not recommended for the treatment of chronic pain. It is a medical food that is a proprietary blend of L-arginine, L-glutamine, choline bitartrate, L-serine and gammaaminobutyricacid [GABA]. See Medical foods.
Triazolam	Not recommended. See Benzodiazepines.
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 (TPIs)	Recommended for myofascial pain syndrome as indicated below, with limited lasting value. The advantage appears to be in enabling patients to undergo remedial exercise therapy more quickly. The primary goal of trigger point therapy is the short-term relief of pain and tightness of the involved muscles in order to facilitate participation in an active rehabilitation program and restoration of functional capacity. TPIs are generally considered an adjunct rather than a primary form of treatment and should not be offered as either a primary or a sole treatment modality. (Scott, 2005) See Myofascial pain. A recent systematic review came to the conclusion that the efficacy of TPIs was no more certain than it was a decade ago, and that there continued to be no clear cut evidence of either benefit or ineffectiveness. There is no evidence-based or consensus research to suggest an optimal technique. The mechanism of inactivation of the trigger point remains unknown. Many consider dry needling as effective as a TPI. It has been suggested that the main effect is placebo. (Cummings, 2001) There are no studies that compare “stretching” treatment alone or “no treatment” to TPIs. Most current studies have evaluated the use of a TPI as a stand-alone treatment. (Scott, 2008) (Staal, 2008)

	Indications: The main indication is to inactivate the trigger point in order to reduce pain and restore function. This may enable physical therapy. The injection is also used as a diagnostic tool. (Scott, 2008) *Whiplash and chronic head, neck, shoulder and back pain:* The evidence for TPIs when used as a sole treatment for patients with whiplash syndrome or chronic head, neck, shoulder or back pain (regardless of injectate) is inconclusive and the treatment does not appear to be more effective than treatments such as laser or ultrasound. These injections are not recommended for typical chronic low back or neck pain, nor are they recommended for radicular pain. *Fibromyalgia:* There is no evidence to support trigger point injections for this condition using randomized controlled trials. Uncontrolled trials suggest that dry needling or soft-tissue injections with lidocaine are equally effective. (Goldenberg, 2004) *Cervicogenic headaches:* The effectiveness is unknown. (Scott, 2005) *Osteoarthritis:* There is one randomized controlled trial that indicates that the addition of TPIs to intra-articular injections improves pain and function over and above the latter injection alone. (Yentur, 2003) *Needling procedures:* The standard definition of TPIs (also called direct wet needling) involves injecting fluid directly into the trigger point. (Cummings, 2001) Other needling techniques include injection of fluid over the trigger point into the skin or subcutaneous tissue, direct dry needling, or indirect dry needling (the needle is placed superficially or deep into classic acupuncture points or over a tender spot, but not into the trigger point). See Acupuncture. *Injection fluids:* The injection of a local anesthetic can reduce the pain of a trigger point. TPIs with an anesthetic such as bupivacaine are recommended for non-resolving trigger points. In addition, the addition of a local anesthetic can reduce the pain of injection. The addition of a corticosteroid is not generally recommended and there is moderate evidence that TPIs with corticosteroids do not produce significantly different results from placebo injections using short-term self reports. Current evidence does not support the use of Botulinum toxin in trigger point injections for myofascial pain. (Ho, 2007) (Peloso, 2007) *Adverse effects:* The following have been published in case reports: cervical epidural abscess; accidental intrathecal injection; muscle atrophy at the injection site; pneumothorax; development of asystole. There is also a concern that when used as a primary therapy patients may become dependent on this treatment, diverting from the underlying factors causing and maintaining pain. (Borg-Stein, 2002) Vasovagal responses are the most frequent complication. Other complications include bleeding, cuts or tears to the muscle, injury to nerve fibers, damage to blood vessels, infection, and allergic reactions (including anaphylaxis). *Contraindications:* Acute cases of muscle trauma; Allergies to anesthetic agents; Bleeding disorders; Local or systemic infection; Anticoagulant use. *Trigger point definitions:* A trigger point is a hyperirritable foci located in a palpable taut band of skeletal muscle, which produces a local twitch in response to stimulus to the band. Pain is generally reported on compression, with common evidence of characteristic referred pain. This may or may not be accompanied by an autonomic response. Trigger points may be present in up to 33-50% of the adult population. There is

	currently no satisfactory objective, biochemical, electromyographic, or diagnostic imaging test to diagnosis trigger points. (Scott, 2008) *Active trigger point:* Continuous pain is generated in the zone of reference with or without palpitation. *Latent trigger point:* No evidence of spontaneous pain but evidence of restricted movement and muscle weakness. *Primary trigger point:* develop independently of other trigger points. *Satellite trigger points:* result from stress and muscle spasm caused by neighboring trigger points. (Scott, 2005) *Myofascial pain syndrome* is a regional painful muscle condition with a direct relationship between a specific trigger point and its associated pain region. A cluster of symptoms is noted including pain, autonomic phenomena and muscle dysfunction. Examples of primary myofascial pain syndrome include tennis elbow, frozen shoulder and chronic tension type headache. Secondary myofascial pain is found in the presence of conditions such as whiplash, TMJ dysfunction, and osteoarthritis. Psychosocial factors may contribute to muscle tension and an increase in pain, in particular, anxiety. (Esenyel, 2000) (Nifosi, 2007) (Altindag, 2008) (Graff-Radford, 2004) (BlueCross BlueShield, 2004) (Nelemans-Cochrane, 2002) **Criteria for the use of TPIs (Trigger point injections):** TPIs with a local anesthetic may be recommended for the treatment of 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) No more than 3-4 injections per session; (6) No repeat injections unless a greater than 50% pain relief with reduced medication use 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)TPIs with any substance (e.g., saline or glucose) other than local anesthetic with or without steroid are not recommended; (9) There should be evidence of continued ongoing conservative treatment including home exercise and stretching. Use as a sole treatment is not recommended; (10) If pain persists after 2 to 3 injections the treatment plan should be reexamined as this may indicate a lack of appropriate diagnosis, a lack of success with this procedure, or a lack of incorporation of other more conservative treatment modalities for myofascial pain. It should be remembered that trigger point injections are considered an adjunct, not a primary treatment.
Tumor necrosis factor (TNF) modifiers	Not recommended. This drug was recently included in a list of 20 medications identified by the FDA's Adverse Event Reporting System which are under FDA investigation. (FDA, 2008) See also relevant MTUS body chapters.
UltraClear	Not recommended for treatment of chronic pain. UltraClear is a medical food that is a proprietary blend of nutrients in a low-allergen-potential rice protein base. See Medical foods.
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)
Urine drug testing (UDT)	See MTUS Opioids Treatment Guidelines for additional information on urine drug testing.
Valium (diazepam)	See Benzodiazepines.
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 inhibitors (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 anticholenergic side effects. Dosage requirements are necessary in patients with hepatic and renal impairment. (Namaka, 2004) See Antidepressants for chronic pain for general guidelines, as well as specific Venlafaxine listing for more information and references.
Vicodin®	See MTUS Opioids Treatment Guidelines Injuries for information on opioids. Also see Hydrocodone/Acetaminophen (Vicodin®).
Vicoprofen®	See MTUS Opioids Treatment Guidelines for information on opioids. Also see Hydrocodone/Ibuprofen (Vicoprofen®).
Vimovo (esomeprazole magnesium/ naproxen)	Not recommended as a first-line therapy. See Proton pump inhibitors (PPIs) & Naproxen. In May 2010 FDA approved Vimovo, a fixed-dose tablet combination of delayed-release enteric-coated naproxen and immediate-release esomeprazole magnesium (Nexium). The NSAID/PPI combo is indicated to relieve signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis while decreasing the risk for NSAID-related gastric ulcers in susceptible patients. (FDA, 2010) As with Nexium, a trial of omeprazole and naproxen or similar combination is recommended before Vimovo therapy.
Vimpat® (lacosamide)	See Lacosamide (Vimpat®).
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)
Vitamin B	Not recommended for the treatment of chronic pain. Vitamin B is frequently used for treating peripheral neuropathy but its efficacy is not clear. A recent meta-analysis concluded that there are only limited data in

	randomized trials testing the efficacy of vitamin B for treating peripheral neuropathy and the evidence is insufficient to determine whether vitamin B is beneficial or harmful. In the comparison of vitamin B with placebo, there was no significant short-term benefit in pain intensity while there is a small significant benefit in vibration detection from oral benfotiamine, a derivative of thiamine. In comparing different doses of vitamin B complex, there was some evidence that higher doses resulted in a significant short-term reduction in pain and improvement in paraesthesiae, in a composite outcome combining pain, temperature and vibration, and in a composite outcome combining pain, numbness and paraesthesiae. There was some evidence that vitamin B is less efficacious than alpha-lipoic acid, cilostazol or cytidine triphosphate in the short-term improvement of clinical and nerve conduction study outcomes. Vitamin B is generally well-tolerated. (Ang-*Cochrane*, 2008)
Vitamin D (cholecalciferol)	Not recommended for the treatment of chronic pain based on recent research below. Although it is not recommended as an isolated pain treatment, vitamin D supplementation is recommended to supplement a documented vitamin deficiency, which is not generally considered a workers' compensation condition. Musculoskeletal pain is associated with low vitamin D levels but the relationship may be explained by physical inactivity and/or other confounding factors. Adjusting for these factors attenuated the relationship, although pain remained moderately associated with increased odds of 20% of having low vitamin D levels. (McBeth, 2010) Inadequate vitamin D may represent an under-recognized source of nociperception and impaired neuromuscular functioning among patients with chronic pain. Physicians who care for patients with chronic, diffuse pain that seems musculoskeletal - and involves many areas of tenderness to palpation - should consider checking vitamin D level. For example, many patients who have been labeled with fibromyalgia may be suffering from symptomatic vitamin D inadequacy. Patients with inadequate vitamin D may benefit from cholecalciferol 50,000 international units dosed according to the level of deficiency, but caution is necessary for patients with calcium- or phosphate- processing disorders because increasing vitamin D levels could be problematic in patients with kidney failure or stones or primary hyperparathyroidism or sarcoidosis. For patients with adequate vitamin D looking to maintain levels, 10 to 15 minutes of sun exposure might be recommended with no sunscreen on the trunk and arms and legs 3 times a week. (Turner, 2008) Recent studies have suggested that vitamin D supplementation is a safe, well-tolerated approach to improve muscle strength and function, leading to fewer falls. This systematic review and meta-analysis demonstrated that there is a protective effect of vitamin D supplementation on fall prevention in older adults. (Kalyani, 2010) On the other hand, most Americans already receive enough vitamin D, according to a report released by the Institute of Medicine, and they concluded that the positive effects of vitamin D haven't been nearly as clear-cut as advocates have suggested. (IOM, 2010) Women who take a single high dose of vitamin D (300,000 IUs) suffer much less menstrual pain and have no need of pain medications for any reason for up to 2 months, according to a new RCT. The authors say

	vitamin D may act as an anti-inflammatory and may regulate the expression of key genes involved in the prostaglandin pathway, causing decreased biological activity of prostaglandins. Although the numbers were small, there was a convincing difference between the placebo and vitamin D groups in the study, but it is premature to recommend this. The 300,000 IU dose of vitamin D used in the study is probably harmless if taken every month or two, but it could cause hypercalcemia if taken daily. (Lasco, 2012) *Recent research:* In this RCT, Vitamin D supplementation for 2 years at a dose sufficient to elevate 25-hydroxyvitamin D plasma levels to higher than 36 ng/mL, when compared with placebo, did not reduce knee pain or cartilage volume loss in patients with symptomatic knee OA. (McAlindon, 2013) Optimization of calcifediol levels in fibromyalgia syndrome had a positive effect on the perception of pain, but further studies with larger patient numbers are needed to prove the hypothesis (Wepner, 2014).
Vitamin K	Not recommended for the treatment of chronic pain. This study concluded that low dietary vitamin K intake is a risk factor for knee OA, and that vitamin K may have a protective role against knee OA and might lead to a disease-modifying treatment. (Oka, 2010) But this study concluded that there was no overall effect of vitamin K on radiographic hand osteoarthritis. (Neogi, 2008) This study found an association between low plasma levels of vitamin K and increased prevalence of OA manifestations in the hand and knee. (Neogi, 2006)
Vivitrol® (naltrexone)	See Naltrexone (Vivitrol®).
Voltaren®	See Diclofenac Sodium (Voltaren®, Voltaren-XR®), where the oral form is recommended with cautions, but not as a first-line drug.
Voltaren® Gel (diclofenac)	Not recommended as a first-line treatment. See Diclofenac Sodium (Voltaren®), where Voltaren Gel is recommended for osteoarthritis after failure of an oral NSAID, or contraindications to oral NSAIDs, or for patients who cannot swallow solid oral dosage forms, and after considering the increased risk profile with diclofenac, including topical formulations. According to FDA MedWatch, postmarketing surveillance of Voltaren Gel has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation. (FDA, 2011) For more details see Topical analgesics, Non-steroidal antinflammatory agents (NSAIDs), and the diclofenac topical listing.
Weaning	See Weaning, benzodiazepines (specific guidelines); Weaning, carisoprodol(Soma®); Weaning, pregabalin (Lyrica®); Weaning, scheduled medications (general guidelines); Weaning, stimulants.
Weaning, benzodiazepines (specific guidelines)	Recommended for selected patients. See Weaning, scheduled medications (general guidelines). There is no specific or internationally recognized treatment for dependence on this class of drugs. Researchers suggest that serious dependence involves individuals who (1) are prescribed this class of drugs for underlying pathology and progress to inappropriate use, or (2) individuals who use this class of drugs for

	recreational use. Serious problematic use includes evidence of mixing benzodiazepines, repeated evidence of escalating doses, or use to enhance effects of other substances. Unfortunately, most current research on weaning of benzodiazepines addresses patients who are not abusing this class of drugs (i.e. are using their medication for legitimate diagnoses with no evidence of abuse). (Liebrenz, 2010) *Guidelines:* Tapering is generally required if used for greater than 2 weeks. The concomitant use of alcohol and/or other sedative hypnotics should be ascertained. A history of anxiety disorder (particularly panic) should be elicited. Medical supervision is recommended for withdrawal as there are significant possible complications. Withdrawal is considered more severe for benzodiazepines with shorter elimination half-life. (Rickels, 1999) (Maremmani, 2013) (Ashton, 2009) (Lingford-Hughes, 2004) (Voshaar, 2006) (Parr, 2009) *Weaning setting:* Outpatient weaning is generally only recommended for patients who are taking drugs in a therapeutic range, who are on monotherapy (benzodiazepines only), are considered reliable and have the help of significant others to monitor progress. *Chance of achieving long-term abstinence:* Due to risks of weaning the most attainable goal may be to simply achieve a lower dose of this class of medication with preference for a switch from rapid onset, short-acting formulations to slower-onset, longer-acting formulations (such as clonazepam). See Benzodiazepine dependence, maintenance. (O'Brien, 2005) (Liebrenz, 2010) (Maremmani, 2013) *Current weaning protocol recommendations:* Weaning of benzodiazepines in general is more dangerous than opioid withdrawal, and takes more time. A step-wise approach is indicated based on limited research. The initial recommendation is to use minimal interventions including advisory letters, education and single-visit doctor's consults addressing use of this class of drugs. The next step is gradual drug reduction. As noted, there is no currently universal weaning protocol available. One current recommendation is the following: (1) The recommended rate of tapering is about 1/8 to 1/10 of the daily dose every 1 to 2 weeks; (2) An alternative weaning schedule is to decrease by 10% a week or 5 mg (whichever is smaller); (3) The first 50% of weaning is generally smoother than the last 50%; (4) When the final 25% to 35% of dose is reached it is suggested that the decrease in dose be lowered to 5% at a two-week interval; (5) Rate of withdrawal should be individually tapered based on signs and symptoms; (6) Visits should occur on a weekly basis during weaning or more often if clinically indicated; (7) Recurrent assessment is required, particularly at the time of dose changes; (8) High-dose abusers or those with polydrug abuse may need in-patient detoxification; & (9) Withdrawal can occur when a chronic user switches to a benzodiazepine with a different receptor activity. A recent review suggests not prolonging weaning for over six months. (Lee, 2002) (TIP 45, 2006) (Lader, 2009) (Morin, 2004) (Alexander, 1991) (Ashton, 1994) It should be noted that the above recommendation for weaning is often not effective for patients taking short-acting benzodiazepines (lorazepam, oxazepam, triazolam, alprazolam and temazepam). A recommendation has been made to switch to a long-acting drug such as chlordiazepoxide or clonazepam or

alternatively, phenobarbital, prior to an attempted wean from these drugs.
Benzodiazepine withdrawal signs and symptoms: These fall into four general categories: (1) Relapse of the symptoms that the drugs were first prescribed for (such as anxiety or insomnia); (2) Rebound of symptoms (a short-duration, intense phenomenon which is self-limited); (3) Pseudowithdrawal (expectations of withdrawal lead to expectations of abstinence); (4) True withdrawal. Prolonged withdrawal has also been described. Seizures are the most worrisome medical complication of withdrawal. Specific signs and symptoms include anxiety, insomnia, restlessness, agitation, irritability and muscle tension. Less frequently reported are nausea, diaphoresis, lethargy, aches and pains, blurred vision, nightmares, depression, hyperreflexia and ataxia. Elderly patients in particular are at risk for delirium, risks of falls, and myocardial infarctions. (TIP 45, 2006) (Dickenson, 2009) (Petursson, 1994)
Adjunct drugs used for weaning from benzodiazepines: Converting to phenobarbital or a long-acting benzodiazepine from a short-acting formulation has been recommended as a step in weaning. Conversion tables are available for specific benzodiazepines to phenobarbital equivalents with recommendations for weaning. (TIP 45, 2006 - figure 4.5) (Dickenson, 2009 - p. 581) Anticonvulsants such as carbamazepine and valproate have been used. (Denis, 2006) (Cluver, 2009)
Equianalgesic doses of benzodiazepines with half-life:
Multiple tables are available suggesting approximate equianalgesic doses. The expanded ranges presented in this table are noted in part where different disease pathology is addressed with the same drug (i.e. addressing anxiety vs. sedation).

Drug	Time to peak onset (hrs)	Half-life (hrs)	Approximate Equivalent Oral Dose (in mgs)
Alprazolam	1-2	6-12	0.5
Chlordiazepoxide	1.5-4	5-30	25
Clonazepam	1-4	18-50	0.25-0.5
Diazepam	1-1.5	20-100	5-10
Flurazepam	1-1.5	40-250	15-30
Lorazepam	2-4	10-20	1
Oxazepam	3-4	4-15	15-20
Temazepam	0.5-3	8-22	10-20
Triazolam	0.5-2	2	0.25 mg

Changing to long-acting formulations: This may take several days, with substitution at intervals, generally starting with the night-time dose.
Comorbid medical conditions and age: The risk of adverse effects due to withdrawal may outweigh long-term benefits of discontinuing benzodiazepines. This is particularly a concern for patients with adrenergic stress factors (i.e. cardiac disease and asthma), or psychologic stress.
Important points to remember: (1) There is a high risk of the use of alcohol in patients taking benzodiazepines.
(2) There is a high risk of anxiety disorders in patients taking benzodiazepines. (3) Withdrawal in elderly patients may be prolonged and the clinician needs to address severity of high-dose withdrawal due to

	pharmacokinetics. (Benzon, 2005) (Ashton, 2005) (Kahan, 2006) (Lader, 2009) (Smith, 1990) (Dickenson, 2009) *Benzodiazepine dependence, maintenance treatment:* Recommended for selected patients. Early research indicates that switching from rapid-onset, short-acting benzodiazepines to slow-onset, long-acting formulations is an option. In some cases this will actually allow for ultimate discontinuation of this class of drugs. Clonazepam is the suggested drug to switch to. It has a slow onset of action, half-life of 18-50 hours, high potency and lack of active metabolites. (Liebrenz, 2010) (Maremmani, 2013)
Weaning, carisoprodol (Soma®)	Recommended for selected patients (the majority). See Weaning, scheduled medications (general guidelines). This medication is metabolized to meprobamate, a schedule C-IV controlled anxiolytic agent. 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. *Weaning:* For patients on low to moderate doses of carisoprodol or for short-term duration a slow taper of 2-4 weeks is recommended. One option for withdrawal for patients using high doses of carisoprodol (particularly for those using the drug in doses over what is prescribed) or for long durations is to switch to phenobarbital with subsequent tapering. A conversion table is available for Soma to phenobarbital equivalents (700 mg to 30 mg, respectively) with recommendations for weaning. (Dickenson, 2009 - p. 581) A maximum suggested 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. *Symptoms of withdrawal:* Thought to be secondary to both withdrawal for carisoprodol and meprobamate. Symptoms consist of insomnia, vomiting, tremors, muscle twitching, anxiety, and ataxia with abrupt cessation of large doses. Hallucinations and delusions may also occur. (Reeves, 2010) (Reeves, 2007) (Boothby, 2003) (Heacock, 2004) (Washington, 2002) (Wright, 2009) See also Weaning, scheduled medications (general guidelines); Detoxification.
Weaning, opioids	See MTUS Opioids Treatment Guidelines on weaning opioids.
Weaning, pregabalin (Lyrica®)	Recommended for selected patients. The manufacturer of this drug recommends weaning over at least one week when used as seizure therapy. There is no formal protocol available to guide in weaning when used for treatment of chronic pain, and the drug is rarely used as a monotherapy. A consensus recommendation of a minimum of weaning over two to four weeks is made when used for chronic pain. See also Weaning, scheduled medications (general guidelines); Detoxification; & Rapid detox.
Weaning, scheduled medications (general guidelines)	Recommended when there is evidence of substance misuse, abuse or addiction, as indicated below. See Substance abuse (tolerance, dependence, addiction) for definitions. While the main indication as related to substance-related disorders is evidence of aberrant drug behaviors, other indications for weaning include the following: (1) Intolerable side effects; (2) Lack of significant symptomatic response to current pain medication treatment (particularly when there is evidence of increasingly

	escalating doses of substances known for dependence); (3) Refractory comorbid psychiatric illness; (4) Lack of sustained functional improvement related to opioid use; and/or (5) Risks exceeding benefits. *Initial Evaluation:* Patients considered for weaning should undergo an assessment of their general medical, psychiatric, surgical and pain treatment history, with education regarding rationale for weaning, symptoms and potential adjunctive agents or alternative treatments. Vital signs should be monitored throughout the weaning process. Urine toxicology screening may be indicated. If performed in a patient with substance-related disorder (abuse, misuse or addiction), a psychiatric evaluation may not reveal an accurate diagnosis until months after weaning is achieved. *Setting for weaning:* Important variables as to the setting in which weaning should occur include the presence of comorbid medical and psychiatric pathology and evidence of use of poly-pharmacy. Medical conditions that may favor inpatient detoxification include a history of significant TBI or seizures (seizure risk, delirium), cardiac disease (sympathetic hypersensitivity), significant liver or kidney disease. Psychiatric conditions potentially favoring inpatient weaning include suicidal or homicidal risks, delirium, and diagnosis of bipolar disorder and other significant psychiatric disease. Patients with alcoholism and history of delirium tremens may merit inpatient treatment. Many of the patients that are recommended for inpatient weaning are using high doses and/or multiple substances that are prescribed, and may also be using other substances such as alcohol and/or illicit substances (street drugs). Benzodiazepines and sedative-hypnotics in particular contribute to increased withdrawal symptoms, including the possibility of seizures, and a less predictable course. More intensive monitoring will be necessary when these variables are present. (TIP 40, 2004) Weaning for specific classes of drugs are listed in the following entries in the Pain Chapter: Weaning, benzodiazepines (specific guidelines); Weaning, carisoprodol (Soma®); Weaning, pregabalin (Lyrica®); Weaning, stimulants.
Weaning, stimulants	Recommended in selected patients (consensus). The stimulant class includes armodafinil, modafinil, methylphenidate, dextroamphetamine, & amphetamine salt combinations. See Weaning, scheduled medications (general guidelines). Stimulant withdrawal is generally not medically life threatening. The most serious problem with withdrawal is that patients may become severely depressed (to the point of suicide), and develop agitation and insomnia. Antidepressant therapy may be required. Withdrawal symptoms develop within hours to days after heavy use. In patients who are abusing this class of drugs, concomitant use of other drugs and/or alcohol should be evaluated for. Patients who are abusing stimulants or show evidence of abuse of multiple substances should be weaned under the direction of a specialist. *Withdrawal signs and symptoms:* Jittery reactions with agitated paranoia; Intense drug craving; Weight loss; Anorexia; Dehydration; Fatigue; Dulled senses; Psychomotor lethargy and retardation with impaired memory; Hunger; Chills; Insomnia followed by hypersomnia; Dysphoric mood; Anxiety; Social withdrawal. (TIP 33, 1999)

	Recommendations for weaning specific drugs in situations where abuse is not suspected (i.e. the drugs are taken as prescribed): - *Armodafinil* (Nuvigil®): There is no recommendation for weaning of this drug by the manufacturer. - *Modafinil* (Provigil®): In one clinical trial withdrawal did not occur with abrupt discontinuation. If given for excessive daytime sleepiness, symptoms may return to baseline. - *Stimulants requiring gradual weaning: Methylphenidate* (Ritalin®, Methylin®, Metadate ER®, Methylin ER®, Ritalin SR®); *Amphetamine salt combo* (Adderall®, Adderall XR®); - *Dextroamphetamine* (Dexedrine®, Dextrostat®, Dexedrine Spansules) Gradual withdrawal over two to four weeks is recommended as abrupt discontinuation can unmask severe depression and precipitate withdrawal. See Weaning, scheduled medications (general 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®).
Work conditioning, work hardening	Recommended as an option for treatment of chronic pain syndromes, depending on the availability of quality programs. Work hardening is an interdisciplinary, individualized, job-specific program of activity with the goal of return to work. The Commission on Accreditation of Rehabilitation Facilities (CARF) provides accreditation to occupational rehabilitation facilities meeting appropriate standards. The effectiveness of physical conditioning as part of a return-to-work strategy in reducing sick leave for workers with back pain, compared to usual care or exercise therapy, remains uncertain. (Schaafsma, 2010) Criteria for admission to a Work Hardening (WH) Program (APTA 2011, Orthopaedic Section BOD, 2011**):** (1) *Prescription:* The program has been recommended by a physician or nurse case manager, and a prescription has been provided. (2) *Screening Documentation:* Approval of the program should include evidence of a screening evaluation. This multidisciplinary examination should include the following components: (a) History including demographic information, date and description of injury, history of previous injury, diagnosis/diagnoses, work status before the injury, work status after the injury, history of treatment for the injury (including medications), history of previous injury, current employability, future employability, and time off work; (b) Review of systems including other non work-related medical conditions; (c) Documentation of musculoskeletal, cardiovascular, vocational, motivational, behavioral, and cognitive status by a physician, chiropractor, or physical and/or occupational therapist (and/or assistants); (d) Diagnostic interview with a mental health provider; (e) Determination of safety issues and accommodation at the place of work injury. Screening should include adequate testing to determine if the patient has attitudinal and/or behavioral issues that are appropriately addressed in a multidisciplinary work hardening program. The testing should also be intensive enough to provide evidence that there are no psychosocial or significant pain behaviors that should be addressed in other types of programs, or will likely prevent successful participation and return-to-

	employment after completion of a work hardening program. Development of the patient's program should reflect this assessment. (3) *Job demands:* A work-related musculoskeletal deficit has been identified with the addition of evidence of physical, functional, behavioral, and/or vocational deficits that preclude ability to safely achieve current job demands. These job demands are generally reported in the medium or higher demand level (i.e., not clerical/sedentary work). There should generally be evidence of a valid mismatch between documented, specific essential job tasks and the patient's ability to perform these required tasks (as limited by the work injury and associated deficits). (4) *Functional capacity evaluations (FCEs):* A valid FCE should be performed, administered and interpreted by a licensed medical professional. The results should indicate consistency with maximal effort, and demonstrate capacities below an employer verified physical demands analysis (PDA). Inconsistencies and/or indication that the patient has performed below maximal effort should be addressed prior to treatment in these programs. (5) *Previous PT:* There is evidence of treatment with an adequate trial of active physical rehabilitation with improvement followed by plateau, with evidence of no likely benefit from continuation of this previous treatment. Passive physical medicine modalities are not indicated for use in any of these approaches. (6) *Rule out surgery:* The patient is not a candidate for whom surgery, injections, or other treatments would clearly be warranted to improve function (including further diagnostic evaluation in anticipation of surgery). (7) *Other contraindications:* There is no evidence of other medical, behavioral, or other comorbid conditions (including those that are non work-related) that prohibits participation in the program or contradicts successful return-to-work upon program completion. (8) *RTW plan:* A specific defined return-to-work goal or job plan has been established, communicated and documented. The ideal situation is that there is a plan agreed to by the employer and employee. The work goal to which the employee should return must have demands that exceed the claimant's current validated abilities. (9) *Program documentation:* The assessment and resultant treatment should be documented and be available to the employer, insurer, and other providers. There should documentation of the proposed benefit from the program (including functional, vocational, and psychological improvements) and the plans to undertake this improvement. The assessment should indicate that the program providers are familiar with the expectations of the planned job, including skills necessary. Evidence of this may include site visitation, videotapes or functional job descriptions. (10) *Further mental health evaluation:* Based on the initial screening, further evaluation by a mental health professional may be recommended. The results of this evaluation may suggest that treatment options other than these approaches may be required, and all screening evaluation information should be documented prior to further treatment planning. (11) *Supervision:* Supervision is recommended under a physician, chiropractor, occupational therapist, or physical therapist with the appropriate education, training and experience. This clinician should

	provide on-site supervision of daily activities, and participate in the initial and final evaluations. They should design the treatment plan and be in charge of changes required. They are also in charge of direction of the staff. (12) *Trial:* 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 improvement in functional abilities. Outcomes should be presented that reflect the goals proposed upon entry, including those specifically addressing deficits identified in the screening procedure. A summary of the patient's physical and functional activities performed in the program should be included as an assessment of progress. (13) *Concurrently working:* The patient who has been released to work with specific restrictions may participate in the program while concurrently working in a restricted capacity, but the total number of daily hours should not exceed 8 per day while in treatment. (14) *Conferences:* There should be evidence of routine staff conferencing regarding progress and plans for discharge. Daily treatment activity and response should be documented. (15) *Voc rehab:* Vocational consultation should be available if this is indicated as a significant barrier. This would be required if the patient has no job to return to. (16) *Post-injury cap:* 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 generally do not improve from intensive work hardening programs. If the worker is greater than one-year post injury a comprehensive multidisciplinary program may be warranted if there is clinical suggestion of psychological barrier to recovery (but these more complex programs may also be justified as early as 8-12 weeks, see Chronic pain programs). (17) *Program timelines:* These approaches are highly variable in intensity, frequency and duration. APTA, AOTA and utilization guidelines for individual jurisdictions may be inconsistent. In general, the recommendations for use of such programs will fall within the following ranges: These approaches are necessarily intensive with highly variable treatment days ranging from 4-8 hours with treatment ranging from 3-5 visits per week. The entirety of this treatment should not exceed 20 full-day visits over 4 weeks, or no more than 160 hours (allowing for part-day sessions if required by part-time work, etc., over a longer number of weeks). A reassessment after 1-2 weeks should be made to determine whether completion of the chosen approach is appropriate, or whether treatment of greater intensity is required. (18) *Discharge documentation:* At the time of discharge the referral source and other predetermined entities should be notified. This may include the employer and the insurer. There should be evidence documented of the clinical and functional status, recommendations for return to work, and recommendations for follow-up services. Patient attendance and progress should be documented including the reason(s) for termination including successful program completion or failure. This would include noncompliance, declining further services, or limited potential to benefit. There should also be documentation if the patient is unable to participate

	due to underlying medical conditions including substance dependence. (19) *Repetition:* Upon completion of a rehabilitation program (e.g., work conditioning, work hardening, outpatient medical rehabilitation, or chronic pain/functional restoration program) neither re-enrollment in nor repetition of the same or similar rehabilitation program is medically warranted for the same condition or injury. **ODG Work Conditioning (WC) Physical Therapy Guidelines** WC amounts to an additional series of intensive physical therapy (PT) visits required beyond a normal course of PT, primarily for exercise training/supervision (and would be contraindicated if there are already significant psychosocial, drug or attitudinal barriers to recovery not addressed by these programs). See also Physical therapy for general PT guidelines. WC visits will typically be more intensive than regular PT visits, lasting 2 or 3 times as long. And, as with all physical therapy programs, Work Conditioning participation does not preclude concurrently being at work. Suggested timelines: 10 visits over 4 weeks, equivalent to up to 30 hours.
Xanax® (Alprazolam)	Not recommended for long-term use. See Alprazolam; & Benzodiazepines. Alprazolam, also known under the trade name Xanax and available generically, is a short-acting drug of the benzodiazepine class used to treat moderate to severe anxiety disorders, panic attacks, and as an adjunctive treatment for anxiety associated with major depression.
Xartemis XR (oxycodone & acetaminophen)	Refer to the MTUS Opioids Treatment Guidelines for recommendations on the use of opioids. The FDA has approved an extended-release combination of oxycodone and acetaminophen (Xartemis XR, Mallinckrodt plc), for patients for whom alternative treatment options are ineffective, not tolerated, or would otherwise be inadequate. The drug has both immediate- and extended-release components to allow pain relief within an hour, with twice-daily dosing. The approved label for Xartemis XR does not include abuse-deterrent language. Oxycodone exposes patients to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. (FDA, 2014) Xartemis XR is not an abuse-deterrent formulation and altering the tablets (e.g., crushing, chewing, dissolving) could lead to a potentially fatal overdose or other serious adverse effects. Xartemis XR is only approved in one strength, which is oxycodone 7.5mg/ acetaminophen 325mg. The addition of acetaminophen may also limit its use in patients with concern for liver toxicity. (Clinical Pharmacology, 2014)
Xeomin	See Botulinum toxin.
Yoga	Recommended as an option for 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 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) Women with fibromyalgia can reduce symptoms of the disease and improve their function by practicing the mind-body techniques of yoga, a new RCT concludes. The results suggested that yoga led to a beneficial shift in how patients cope with pain, including greater use of adaptive pain-coping

	strategies, such as engaging in activities despite pain, acceptance of their condition, the use of religion as a coping mechanism, and the ability to relax. (Carson, 2010) This meta-analysis suggests that yoga is a useful supplementary approach with moderate effect sizes on pain and associated disability, and even short-term interventions might be effective. (Büssing, 2012) *Mindfulness meditation:* Mind-body medicine (MBM) therapies broadly include meditation, hypnosis, guided imagery, relaxation therapies, biofeedback, spiritual healing, yoga, tai chi, qigong, art therapy, light therapy, and others. Mindfulness is defined as a nonjudgmental moment-to-moment awareness, including mindful movement (body awareness during yoga postures). The medical literature on mindfulness-based stress reduction (MBSR) is favorable, especially for chronic pain, anxiety, and general psychologic health; however, many of the studies are self-controlled, comparing a patient's pretreatment symptoms with posttreatment. In a study examining chronic pain patients, with mean duration of pain of 8.1 years, including of low back pain, headache, and neck/shoulder pain, patients were evaluated before and after the 8-week intervention, then for 48 months in follow-up. Of patients, 60% to 72% reported moderately or greatly decreased pain, decreased psychologic symptoms, and decreased general medical complaints. 86% responded affirmatively the program. Gains in medical and psychologic symptoms were maintained at 4-year follow-up. (Barrows, 2002) For mindfulness meditation, see Behavioral interventions/Cognitive Behavioral Therapy (CBT). Also see relevant MTUS body chapters
Zanaflex® (tizanidine)	Zanaflex® is a muscle relaxant. See Muscle relaxants. See also specific Tizanidine (Zanaflex®) listing.
Ziconotide (Prialt®)	Recommended for use after there is evidence of failure of a trial of intrathecal morphine or hydromorphone (Dilaudid). Indicated for the management of severe chronic pain in patients for whom intrathecal therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies or IT morphine, and only in individuals for whom the potential benefits outweigh the risks of serious neuropsychiatric adverse effects. 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 or 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 *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 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. For subsequent pump refills, fill the pump at least every 40 days if used diluted. For undiluted Prialt, fill the pump at least every 84 days. *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) Intrathecal ziconotide may increase risk for suicide. Researchers are calling for a comprehensive psychiatric evaluation in all patients before and during treatment, but ziconotide may pose a threat even in symptom-free patients with pain. Better monitoring of all patients on this medication is necessary, and strict compliance to the contradictions such as a history of depression is key. Ziconotide not only suppresses the transmission of pain stimuli but may also reduce impulse control, promoting suicidal tendencies in vulnerable patients. (Maier, 2010).
Zipsor (diclofenac potassium liquid-filled capsules)	Not recommend diclofenac as first line due to increased risk profile. See Diclofenac listing. Zipsor diclofenac potassium liquid-filled capsules (Xanodyne) were approved by the FDA in June 2009. (FDA, 2009) When compared with absorption characteristics of diclofenac potassium tablets, Zipsor was more rapidly absorbed after bunionectomy, which may be advantageous if rapid pain relief is required, but there were no other advantages over the tablets. (Kowalski, 2009) In dental surgery patients Zipsor provided rapid onset of confirmed perceptible pain relief within 30 minutes of administration. (Zuniga, 2011) See Diclofenac Potassium.
Zohydro®	Not recommended. Refer to the MTUS Opioids Treatment Guidelines for recommendations on the use of opioids. See Hydrocodone. Zohydro ER (Zogenix Inc) is the first single-entity extended-release (ER) formulation of

	hydrocodone approved by the FDA; unlike Vicodin, Lortab and Norco, it is not buffered with acetaminophen or some other OTC medication. Each pill will be very potent, but Zohydro does not have abuse-deterrent technology. According to the FDA, Zohydro ER should be reserved for use in patients for whom alternative treatment options are ineffective. FDA's Drug Advisory Committee of independent experts voted 11 to 2 to recommended against approval of Zohydro for the treatment of moderate to severe chronic pain because of the potential for abuse of this drug.
Zolpidem (Ambien®)	Zolpidem is a prescription short-acting nonbenzodiazepine hypnotic, which is approved for the short-term (usually two to six weeks) treatment of insomnia. Proper sleep hygiene is critical to the individual with chronic pain and often is hard to obtain. Various medications may provide short-term benefit. While sleeping pills, so-called minor tranquilizers, and anti-anxiety agents are commonly prescribed in chronic pain, pain specialists rarely, if ever, recommend them for long-term use. They can be habit-forming, and they may impair function and memory more than opioid pain relievers. There is also concern that they may increase pain and depression over the long-term. (Feinberg, 2008) See Insomnia treatment. Ambien CR offers no significant clinical advantage over regular release zolpidem. Ambien CR is approved for chronic use, but chronic use of hypnotics in general is discouraged, as outlined in Insomnia treatment. Ambien CR causes a greater frequency of dizziness, drowsiness, and headache compared to immediate release zolpidem. (Ambien & Ambien CR package insert) Cognitive behavioral therapy (CBT) should be an important part of an insomnia treatment plan. A study of patients with persistent insomnia found that the addition of zolpidem immediate release to CBT was modestly beneficial during acute (first 6 weeks) therapy, but better long-term outcomes were achieved when zolpidem IR was discontinued and maintenance CBT continued. (Morin, 2009) Due to adverse effects, FDA now requires lower doses for zolpidem. The dose of zolpidem for women should be lowered from 10 mg to 5 mg for IR products (Ambien, Edluar, Zolpimist, and generic) and from 12.5 mg to 6.25 mg for ER products (Ambien CR). The ER product is still more risky than IR. In laboratory studies, 15% of women and 3% of men who took a 10-milligram dose of Ambien had potentially dangerous concentrations of the drug in their blood eight hours later. Among those who took Ambien CR, the problem was more common: 33% of women and 25% of men had blood concentrations that would raise the risk of a motor vehicle accident eight hours later. Even at the lower dose of Ambien CR now recommended by the FDA, 15% of women and 5% of men still had high levels of the drug in their system in the morning. (FDA, 2013) According to SAMHSA, zolpidem is linked to a sharp increase in ED visits, so it should be used safely for only a short period of time.
Zonisamide (Zonegran®)	See Anti-epilepsy drugs (AEDs) for general guidelines, as well as specific Zonisamide listing.
Zorvolex® (diclofenac)	Not recommended except as a second-line option, because diclofenac products are not recommended as first-line choices due to potential increased adverse effects. See Diclofenac. In late 2013 FDA approved

	diclofenac capsules (Zorvolex, Iroko Pharmaceuticals LLC) at 18-mg and 35-mg doses for the treatment of mild to moderate acute pain in adults. These dosages are 30% lower in strength than the 25-mg and 50-mg diclofenac products already on the market. The FDA also approved another lower-dose NSAID from Iroko Pharmaceuticals, indomethacin capsules (Tivorbex). While diclofenac has potent anti-inflammatory and analgesic properties, research has linked this drug to sometimes serious adverse outcomes, including cardiovascular thrombotic events, myocardial infarction, stroke, gastrointestinal ulcers, gastrointestinal bleeding, and renal events (such as acute renal failure). (FDA, 2014) This new formulation of diclofenac does not present any apparent advantages versus other medications of the class. Zorvolex is pure acid versus salt in other formulations, resulting in faster dissolution using SoluMatrix Fine Particle Technology. However, it has the same side effect profile while more expensive than other NSAIDs that are available as generics. It is an expensive, brand name only, second-line medication with little to no place in the treatment of workers compensation injuries. (FDA, 2013)
Zubsolv® (buprenorphine/ naloxone)	Zubsolv (buprenorphine and naloxone), a recently FDA-approved medication for maintenance treatment of opioid dependence, is a once-daily sublingual tablet that offers higher bioavailability that allows patients to use lower strength and reduce the amount of available drug for potential misuse and diversion. (FDA, 2013) See Buprenorphine.

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Low Priority References

LOW BACK PAIN

Sommer HM. The Patient in Jeopardy: How the Low Back Pain Patient Becomes Disabled. *Occupational Medicine* 1998;(13)1:23-31.

PAIN – CHRONIC

Gallagher RM. Primary care and pain medicine. A community solution to the public health problem of chronic pain. *Medical Clinics of North America*. 01-May-1999; 83(3): 555-83, v.

PAIN – MISCELLANEOUS

Robinson JP, Fulton-Keohe D, Martin C, Franklin GM. Outcomes of Pain Center Treatment in Washington State Workers' Compensation. Am J Ind Med 2001;227-236.

PSYCHOSOCIAL EVALUATION AND TREATMENT

Goldberg RT; Pachas WN; Keith D. Relationship between traumatic events in childhood and chronic pain. *Disability Rehabilitation.* 01-Jan-1999; 21(1): 23-30.

McCracken LM, Matthews AK, Tang TS, Cuba SL. A comparison of blacks and whites seeking treatment for chronic pain. *Clinical Journal of Pain*. 2001 Sep;17(3):249-55.

Pulliam CB, Gatchel RJ, Gardea MA. Psychosocial differences in high risk versus low risk acute low-back pain patients. Journal of Occupational Rehabilitation. 2001 Mar;11(1):43-52.

Severeijns R; Vlaeyen JW; van den Hout MA; Weber WE. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *Clinical Journal of Pain.* 01-Jun-2001; 17(2): 165-72.

THERAPEUTIC INTERVENTION

Gallagher RM. Treatment planning in pain medicine. Integrating medical, physical, and behavioral therapies. *Medical Clinics of North America.* 01-May-1999; 83(3): 823-49, viii.

References for Procedure Summary

NOTE: Refer to Explanation of ODG Medical Literature Ratings for a description of ODG's evidence rating.

Abejón D, Garcia-del-Valle S, Fuentes ML, Gómez-Arnau JI, Reig E, van Zundert J. Pulsed radiofrequency in lumbar radicular pain: clinical effects in various etiological groups. *Pain Pract*. 2007 Mar;7(1):21-6.

METHODS: A retrospective analysis of 54 consecutive patients. RESULTS: A decrease in the NRS score was observed in patients with HD ($P < 0.05$) and SS ($P < 0.001$), but not in those with FBSS.

PMID: 17305674

Rating: 4c

"this option does not appear to be an ideal modality of treatment for LRP because neurodestructive methods for the treatment of neuropathic pain are in principle generally considered inappropriate.... Authors noted this is a small retrospective study and prospective randomized studies are needed to confirm the findings before adding pulsed radiofrequency to the armamentarium for lumbar radicular pain treatment.

Ackerman WE, Zhang JM. Efficacy of stellate ganglion blockade for the management of type 1 complex regional pain syndrome. *South Med J.* 2006 Oct;99(10):1084-8.

Pain Medicine Consultants PA, Little Rock, AR, USA. William.Ackerman@bhsi.com

METHODS: 25 subjects. RESULTS: Compared with the normal control hand, the skin perfusion in the CRPS I affected hand was greater in group I and decreased in groups II and III. DISCUSSION: The results of our study demonstrate that an inverse relationship exists between hand perfusion and the duration of symptoms of CRPS I. On the other hand, a positive correlation exists between SGB efficacy and how soon SGB therapy is initiated. A 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 affects the efficacy of SGB therapy.

PMID: 17100029

Rating: 4c

Adams H, Ellis T, Stanish WD, Sullivan MJ. Psychosocial factors related to return to work following rehabilitation of whiplash injuries. *J Occup Rehabil.* 2007 Jun;17(2):305-15.

PMID: 17486435

Rating: 3b

Aetna Clinical Policy Bulletins. Chronic Pain Programs Number 0237. Reviewed: May 5, 2006.

Aetna considers a screening examination medically necessary for members who are being considered for admission into a chronic pain program.

Rating: 8b

Aetna Clinical Policy Bulletins. Electrical Stimulation for Pain. Number 0011. February 22, 2005. Updated 2007.

Aetna considers transcutaneous electrical nerve stimulators (TENS) medically necessary durable medical equipment (DME) when used as an adjunct or as an alternative to the use of drugs in the treatment of acute post-operative pain in the first 30 days after surgery, or chronic, intractable pain not responsive to other methods of treatment.

Rating: 8b

Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, Mannion AF, Reis S, Staal JB, Ursin H, Zanoli G; On behalf of the COST B13 Working Group on Guidelines for Chronic Low Back Pain. Chapter 4 European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J*. 2006 Mar;15(Supplement 2):s192-s300.

PMID: 16550448

Rating: 8a

Altindag O, Gur A, Altindag A. The relationship between clinical parameters and depression level in patients with myofascial pain syndrome. *Pain Med*. 2008;9:161-5.

RESULTS: Major depression was more frequently found in CPPs with MPS ($P < 0.001$). BDI scores were higher in the MPS group than in controls ($P < 0.001$). There was a significant correlation between the severity of pain and depression level in patients with MPS ($r = 0.654$, $P < 0.001$).

PMID: 18298698

Rating 3b

Alvarez DJ, Rockwell PG. Trigger points: diagnosis and management. *Am Fam Physician*. 2002 Feb 15;65(4):653-60.

Trigger-point injection has been shown to be one of the most effective treatment modalities to inactivate trigger points and provide prompt relief of symptoms.

PMID: 11871683

Rating: 5b

American Academy of Pain Medicine. Use of Opioids for the Treatment of Chronic Pain. (February 6, 2001).

These publications, which have been endorsed by AAPM and APS, state that opioids, sometimes called "narcotic analgesics", are an essential part of a pain management plan. There is currently no nationally accepted consensus for the treatment of chronic pain not due to cancer, yet the economic and social costs of chronic pain are substantial, with estimates ranging in the tens of billions of dollars annually.

Rating: 5b

Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther*. 2011 Dec;90(6):844-51. doi: 10.1038/clpt.2011.188. Epub 2011 Nov 2.

Cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.

PMID: 22048225

Rating: 3c

Abs R, Verhelst J, Maeyaert J, Van Buyten JP, Opsomer F, Adriaensen H, Verlooy J, Van Havenbergh T, Smet M, Van Acker K. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab*. 2000;85:2215-22.

Decreased libido or impotency was present in 23 of 24 men receiving opioids. The serum testosterone level was below 9 nmol/L in 25 of 29 men and was significantly lower than that in the control group ($P < 0.001$). The serum LH level was less than 2 U/L in 20 of 29 men and was significantly lower than that in the control group ($P < 0.001$). Serum FSH was comparable in both groups. Decreased libido was present in 22 of 32 women receiving opioids. All 21 premenopausal females developed either amenorrhea or an irregular menstrual cycle, with ovulation in only 1. Supplementation with gonadal steroids improved sexual function in most patients. These findings suggest that further investigations are required to determine the need for systematic endocrine work-up in these patients and the necessity for substitutive therapy.

PMID: 10852454

Rating: 3c

Ackerman LL, Follett KA, Rosenquist RW. Long-term outcomes during treatment of chronic pain with intrathecal clonidine or clonidine/opioid combinations. *J Pain Symptom Manage*. 2003 Jul;26(1):668-77.

Department of Neurosurgery, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242, USA.

15 patients. In this population, intrathecal clonidine was of limited utility for most patients.

PMID: 12850649

Rating: 5b

Ackermann, L., Follett, K., Rosenquist, R. "Long-Term Outcomes During Treatment of Chronic Pain with Intrathecal Clonidine or Clonidine/Opioid Combinations" *Journal of Pain and Symptom Management.* 2003; July, Volume 26: 668-76.

PMID: 12850649

Rating: 2c

Quality: Low. Total Rating: 1.0. Comment: Does not meet inclusion criteria for evidence-based review.

Adams RJ, Appleton SL, Gill TK, Taylor AW, Wilson DH, Hill CL. Cause for concern in the use of non-steroidal anti-inflammatory medications in the community--a population-based study. *BMC Fam Pract*. 2011 Jul 7;12:70.

There is a high prevalence of current NSAID use among groups at-risk for significant drug-related adverse events or who have major chronic conditions that are relative contraindications to NSAID use.

PMID: 21733195

Rating: 3a

Affaitati G, Fabrizio A, Savini A, Lerza R, Tafuri E, Costantini R, Lapenna D, Giamberardino MA. A randomized, controlled study comparing a lidocaine patch, a placebo patch, and anesthetic injection for treatment of trigger points in patients with myofascial pain syndrome: evaluation of pain and somatic pain thresholds*. Clin Ther*. 2009;31:705-20.

RESULTS: Sixty white patients were studied. Subjective symptoms did not change with placebo, but decreased significantly with the lidocaine patch and infiltration relative to baseline.

PMID: 19446144

Rating: 2b

The authors indicated that long-term effect remained to be determined

Afilalo M, Etropolski MS, Kuperwasser B, Kelly K, Okamoto A, Van Hove I, Steup A, Lange B, Rauschkolb C, Haeussler J. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig.* 2010;30(8):489-505.

METHODS: A total of 1030 patients. CONCLUSION: treatment with Tapentadol ER 100-250 mg twice daily or oxycodone HCl CR 20-50 mg twice daily was effective for the management of moderate to severe chronic osteoarthritis-related knee pain, with substantially lower incidences of gastrointestinal-related TEAEs associated with treatment with Tapentadol ER than with oxycodone CR.

PMID: 20586515

Rating: 2a

AGS (American Geriatrics Society) 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012 Apr;60(4):616-31. doi: 10.1111/j.1532-5415.2012.03923.x.

Potentially inappropriate medications (PIMs) continue to be prescribed and used as first-line treatment for the most vulnerable of older adults, despite evidence of poor outcomes from the use of PIMs in older adults.

PMID: 22376048

Rating: 1a

Rating: 9a

Akeson WH, Amiel D, Abel MF, Garfin SR, Woo SL. Effects of immobilization on joints. *Clin Orthop Relat Res*. 1987;:28-37.

PMID: 3581580

Rating: 5c

Albazaz R, Wong YT, Homer-Vanniasinkam S. Complex regional pain syndrome: a review. *Ann Vasc Surg.* 2008;22:297-306.

PMID: 18346583

Rating: 1b

Albert S, Brason FW 2nd, Sanford CK, Dasgupta N, Graham J, Lovette B. Project Lazarus: community-based overdose prevention in rural North Carolina. Pain Med. 2011;12:S77-85.

PMID: 21668761

Rating: 11a

Alexander B, Perry PJ. Detoxification from benzodiazepines: schedules and strategies*. J Subst Abuse Treat*. 1991;8:9-17.

Low-dose withdrawal includes patients who have received manufacturer-recommended doses of BZD on a daily basis for longer than 1 month. Gradual tapering of the BZD over 4 weeks on an outpatient basis is suggested. High-dose withdrawal includes patients who have been ingesting doses of BZD greater than the equivalent of diazepam 40 mg/d for longer than 8 months. It is recommended that the patients be tolerance tested with diazepam and, if tolerant, tapered off medication as inpatients at a rate of 10% per day.

PMID: 1675694

Rating: 5c

Alford DP, Labelle CT, Kretsch N, Bergeron A, Winter M, Botticelli M, Samet JH. Collaborative care of opioid-addicted patients in primary care using buprenorphine: five-year experience. *Arch Intern Med.* 2011 Mar 14;171(5):425-31.

RESULTS: From September 1, 2003, through September 30, 2008, 408 patients with opioid addiction were treated with buprenorphine. At 1 year, 51.3% underwent successful treatment. Of patients remaining in treatment at 12 months, 91.1% were no longer using illicit opioids or cocaine based on urine drug test results.

PMID: 21403039

Rating: 3a

Altmaier EM, Lehmann TR, Russell DW, Weinstein JN, Kao CF. The effectiveness of psychological interventions for the rehabilitation of low back pain: a randomized controlled trial evaluation. *Pain*. 1992 Jun;49(3):329-35.

Division of Psychological and Quantitative Foundations, University of Iowa, Iowa City 52242.

Forty-five low back pain patients. 81% of the patients had returned to work or were engaged in active job retraining by the follow-up. Patient improvement, however, was not differentially affected by treatment group assignment, suggesting that the psychological treatment failed to add to the effectiveness obtained by the standard rehabilitation program.

PMID: 1408299

Rating: 2b

Altman RD, Aven A, Holmburg CE, Pfeifer LM, Sack M, Young GT. Capsaicin Cream 0.025% as Monotherapy for Osteoarthritis: A Double-Blind Study. *Seminars in Arthritis and Rheumatism*, June 1994;23: Suppl 3:25-33.

Patients (113). These results support the beneficial effects of 0.025% capsaicin cream as a first-line therapy for OA pain.

Rating 2c

Altman R, Barkin RL. Topical therapy for osteoarthritis: clinical and pharmacologic perspectives. *Postgrad Med*. 2009 Mar;121(2):139-47.

Neither salicylates nor capsaicin have shown significant efficacy in the treatment of OA. Topical diclofenac sodium 1% gel delivers effective diclofenac concentrations in the affected joint with limited systemic exposure.

PMID: 19332972

Rating: 5b

Altman RD, Barthel HR. Topical therapies for osteoarthritis*. Drugs*. 2011;71:1259-79.

The EULAR and NICE guidelines state that topical NSAIDs should be considered before oral therapies.

PMID: 21770475

Rating: 5c

American College of Medical Quality, acmq.org , Policy 30: Skilled vs. Custodial Care, 2005.

Rating: 8a

American Diabetes Association American Academy of Neurology. Consensus statement: Report and recommendations of the San Antonio conference on diabetic neuropathy. *Diabetes Care.* 1988 Jul-Aug;11(7):592-7.

What Is Diabetic Neuropathy? Diabetic neuropathy is a nerve disorder caused by diabetes. Symptoms of neuropathy include numbness and sometimes pain in the hands, feet, or legs.

PMID: 3060328

Rating: 5a

American Geriatrics Society (AGS). 2009 Annual Scientific Meeting. April 29 - May 03, 2009; Chicago, Illinois. AGS Panel on Pharmacological Management of Persistent Pain in Older Persons.

Revised practice guidelines on the management of persistent pain in the elderly issued by the American Geriatrics Society (AGS) advise physicians to have their patients avoid non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors and consider the use of low-dose opioid therapy instead. The panel concluded that the risks of NSAIDs in older patients, which include increased cardiovascular risk and gastrointestinal toxicity, usually outweigh the benefits and the revised guidelines reflect this. The author pointed out that "a lot of physicians are frightened sometimes to start down that road of giving opioids for chronic pain, especially noncancer-related pain, so in some circles it is controversial."

Rating: 10a

Ang CD, Alviar MJ, Dans AL, Bautista-Velez GG, Villaruz-Sulit MV, Tan JJ, Co HU, Bautista MR, Roxas AA. Vitamin B for treating peripheral neuropathy. *Cochrane Database Syst Rev*. 2008 Jul 16;(3):CD004573.

BACKGROUND: Vitamin B is frequently used for treating peripheral neuropathy but its efficacy is not clear. RESULTS: Thirteen studies involving 741 participants with alcoholic or diabetic neuropathy were included. CONCLUSIONS: There are only limited data in randomised trials testing the efficacy of vitamin B for treating peripheral neuropathy and the evidence is insufficient to determine whether vitamin B is beneficial or harmful.

PMID: 18646107

Rating: 1b

Angel IF, Gould HJ Jr, Carey ME. Intrathecal morphine pump as a treatment option in chronic pain of nonmalignant origin. *Surg Neurol*. 1998 Jan;49(1):92-8; discussion 98-9.

BACKGROUND: Implantable pumps for the delivery of intrathecal morphine have become a common option for administering opiate medication for the management of pain in patients with terminal cancer. Options for treating chronic pain of non-malignant origin are more controversial. METHODS: Eleven patients. CONCLUSIONS: The morphine pump was found to be a viable alternative in the management of failed back syndrome. Its use in long-term therapy, however, is not without limitations and should be a last choice option.

PMID: 9428901

Rating: 4c

Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of Nonsteroidal Antiinflammatory Drugs. An Update for Clinicians. A Scientific Statement From the American Heart Association. *Circulation*. 2007 Feb 26.

PMID: 17325246

Rating: 6a

From Medscape:
The AHA recommends acetaminophen and aspirin as the best initial choices for analgesia of musculoskeletal pain. NSAIDs should be used at the smallest dose for the shortest course possible, and COX-2 inhibitors should be avoided if there is an alternative analgesic available. starting with nonpharmacologic treatments, such as physical therapy and exercise, weight loss to reduce stress on joints, and heat or cold therapy. If this does not provide enough pain relief, acetaminophen, aspirin, and even short-term use of narcotic analgesics are recommended as first-line drugs. Then,
Some Question Narcotics as First-Line Treatment
While all appear to support the recommendation that COX-2 inhibitors should be last on the list, some experts have questioned the advice to give a narcotic before a non-COX-2 selective NSAID, particularly naproxen.

Appelboom T. Calcitonin in reflex sympathetic dystrophy syndrome and other painful conditions. *Bone*. 2002 May;30(5 Suppl):84S-86S.

Division of Rheumatology and Physical Medicine, Erasmus University Hospital, University of Brussels, Brussels, Belgium. tappelbo@ulb.ac.be

Salmon calcitonin (especially intranasal) provides an interesting analgesic effect in a series of painful conditions including reflex sympathetic dystrophy syndrome.

PMID: 12008165

Rating: 5b

American Physical Therapy Association (APTA). Orthopaedic Section BOD. *Occupational Health Physical Therapy: Evaluating Functional Capacity Guidelines*. 2011

Rating: 8a

Argoff CE. Topical agents for the treatment of chronic pain. *Curr Pain Headache Rep*. 2006 Feb;10(1):11-9.

Unlike systemic analgesics, topical analgesics exert their analgesic activity locally and without significant systemic absorption. This is in contrast to transdermal analgesics,

PMID: 16499825

Rating: 5b

Argoff CE, Katz N, Backonja M. Treatment of postherpetic neuralgia: a review of therapeutic options. *J Pain Symptom Manage.* 2004;28:396-411.

Postherpetic neuralgia (PHN) is a disabling consequence of the reactivation of the varicella zoster infection. Physicians can either add another agent to the current regimen or switch to a new type of monotherapy if there is inadequate response to initial therapy.

PMID: 15471658

Rating: 5b

Argoff CE, Galer BS, Jensen MP, Oleka N, Gammaitoni AR. Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: assessment with the Neuropathic Pain Scale. *Curr Med Res Opin*. 2004;20 Suppl 2:S21-8.

CONCLUSIONS: In patients with moderate-to-severe LBP, 2 weeks and 6 weeks of treatment with the lidocaine patch 5% significantly reduces the intensity of pain qualities as measured by all 4 NPS composite measures.

PMID: 15563741

Rating: 4c

Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE Jr, Welge JA, Bishop F, Stanford KE, Hess EV, Hudson JI. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum.* 2007 Apr;56(4):1336-44.

METHODS: A 12-week, randomized, double-blind study was designed to compare gabapentin (1,200-2,400 mg/day) (n=75 patients) with placebo (n=75 patients) RESULTS: Gabapentin-treated patients displayed a significantly greater improvement in the BPI average pain severity score.

PMID: 17393438

Rating: 2a

American Society of Addiction Medicine (ASAM). Public policy statement on rapid and ultra rapid opioid detoxification (Formerly Public Policy Statement on Opioid Antagonist Agent Detoxification under Sedation or Anesthesia (OADUSA). www.asam.org. April 2005.

1. Opioid detoxification alone is not a treatment of opioid addiction. ASAM does not support the initiation of acute opioid detoxification interventions unless they are part of an integrated continuum of services that promote ongoing recovery from addiction.
2. Ultra-Rapid Opioid Detoxification (UROD) is a procedure with uncertain risks and benefits, and its use in clinical settings is not supportable until a clearly positive risk-benefit relationship can be demonstrated. Further research on UROD should be conducted.
3. Although there is medical literature describing various techniques of Rapid Opioid Detoxification (ROD), further research into the physiology and consequences of ROD should be supported so that patients may be directed to the most effective treatment methods and practices.
4. Prior to participation in any particular modality of opioid detoxification, a patient should be provided with sufficient information by which to provide informed consent, including information about the risks of termination of a treatment plan of prescribed agonist medications such as methadone or Buprenorphine, as well as the need to comply with medical monitoring of their clinical status for a defined period of time following the procedure to ensure a safe outcome. Patients should also be informed of the risks, benefits and costs of alternative methods of treatment available.

Rating: 6b

Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain.* 2005 Dec 15;119(1-3):5-15.

354 female patients. In conclusion, both duloxetine 60 mg QD and duloxetine 60 mg BID were effective and safe in the treatment of fibromyalgia in female patients with or without major depressive disorder.

PMID: 16298061

Rating: 2a

Arnold LM. Duloxetine and other antidepressants in the treatment of patients with fibromyalgia. *Pain Med*. 2007;8:S63-74.

DESIGN: Two randomized, placebo-controlled, double-blind, parallel-group, 12-week trials of duloxetine in the treatment of fibromyalgia were reviewed. RESULTS: Duloxetine has been shown to be an effective and safe treatment for many of the symptoms associated with fibromyalgia, particularly for women. CONCLUSIONS: Antidepressants play an important role in the treatment of patients with fibromyalgia. Agents with dual effects on serotonin and norepinephrine appear to have more consistent benefits than selective serotonin antidepressants for the treatment of persistent pain associated with fibromyalgia.

PMID: 17714117

Rating: 5a

Asfour SS, Khalil TM, Waly SM, Goldberg ML, Rosomoff RS, Rosomoff HL. Biofeedback in back muscle strengthening. *Spine*. 1990 Jun;15(6):510-3.

The results obtained indicate that the proposed methodology was an effective tool to achieve a significant improvement in the strength of lumbar paraspinal muscles of chronic low-back pain patients.

PMID: 2144915

Rating: 2c

The study included 30 patients, and found that the increase in strength was greater in the biofeedback group (81.3%) versus the control group (16.9%).

Ashton H. The diagnosis and management of benzodiazepine dependence. *Curr Opin Psychiatry*. 2005 May;18(3):249-55.

PMID: 16639148

Rting: 5b

Ashton H. The treatment of benzodiazepine dependence. *Addiction.* 1994;89:1535-41.

The benzodiazepine dosage should be tapered at an individually titrated rate which should usually be under the patient's control. Unwilling patients should not be forced to withdraw.

PMID: 7841868

Rating: 5c

Ashton CH. Review: brief interventions, gradual dose reduction and psychological interventions increase benzodiazepine cessation compared with routine care. *Evid Based Ment Health.* 2009;12:91. doi: 10.1136/ebmh.12.3.91.

PMID: 19633259

Rating: 2b

Asnis GM, Kohn SR, Henderson M, Brown NL. SSRIs versus non-SSRIs in post-traumatic stress disorder: an update with recommendations. *Drugs*. 2004;64(4):383-404.

Post-traumatic stress disorder (PTSD) is a highly prevalent (7.8% lifetime rate) anxiety disorder with impairment in daily functioning, frequent suicidal behaviour and high rates of co-morbidity. Besides being the most studied and effective drugs for PTSD, SSRIs have a favourable adverse effect profile, making them the first-line treatment for PTSD. Benzodiazepines were ineffective in a double-blind, placebo-controlled study despite encouraging case reports. They should be avoided or used only short term because of potential depressogenic effects, and the possibility that they may promote or worsen PTSD.

PMID: 14969574

Rating: 5b

Astin JA, Shapiro SL, Eisenberg DM, Forys KL, Mind-body medicine: state of the science, implications for practice, *J Am Board Fam Pract.* 2003 Mar-Apr;16(2):131-47.

BACKGROUND: Although emerging evidence during the past several decades suggests that psychosocial factors can directly influence both physiologic function and health outcomes. METHODS: RESULTS: Drawing principally from systematic reviews and meta-analyses, there is considerable evidence of efficacy for several mind-body therapies in the treatment of coronary artery disease (eg, cardiac rehabilitation), headaches, insomnia, incontinence, chronic low back pain.

PMID: 12665179

Rating: 1c

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer TT, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 Jun 19;328(7454):1490.

Judgments about the strength of a recommendation require consideration of the balance between benefits and harms, the quality of the evidence, translation of the evidence into specific circumstances, and the certainty of the baseline risk. It is also important to consider costs (resource utilisation) before making a recommendation.

PMID: 15205295

Rating: 5b

Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS, Nurmikko T, Sampaio C, Sindrup S, Wiffen P; EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006;13:1153-69.

Most of the randomized controlled trials included patients with postherpetic neuralgia (PHN) and painful polyneuropathies (PPN) mainly caused by diabetes. These trials provide level A evidence for the efficacy of tricyclic antidepressants, gabapentin, pregabalin and opioids, with a large number of class I trials, followed by topical lidocaine (in PHN) and the newer antidepressants venlafaxine and duloxetine (in PPN). The main peripheral pain conditions respond similarly well to tricyclic antidepressants, gabapentin, and pregabalin, but some conditions, such as HIV-associated polyneuropathy, are more refractory.

PMID: 17038030

Rating: 1A

Aydin G, Tomruk S, Keles I, Demir SO, Orkun S. Transcutaneous electrical nerve stimulation versus baclofen in spasticity: clinical and electrophysiologic comparison. *Am J Phys Med Rehabil.* 2005 Aug;84(8):584-92.

DESIGN: Patients with spinal cord injury and spasticity were included in the study. Ten patients were assigned to oral baclofen and 11 to TENS groups. For the comparison of H-reflex variables, 20 healthy individuals were allocated to a control group. The percentage change in clinical, electrophysiologic, and functional variables caused by baclofen was not different from that caused by repeated applications of TENS in the short- and long-term evaluations (P > 0.05). CONCLUSION: TENS may be recommended as a supplement to medical treatment in the management of spasticity.

PMID: 16034227

Rating: 2c

Backonja MM, Serra J. Pharmacologic management part 1: better-studied neuropathic pain diseases. *Pain Med*. 2004;5:S28-47.

This review summarizes the published results of randomized trials involving treatment for neuropathic pain conditions.

PMID: 14996228

Rating: 5a

Backonja MM. Use of anticonvulsants for treatment of neuropathic pain. *Neurology*. 2002. 10:59:s14-7.

Lamotrigine has been reported to be effective in relieving pain from trigeminal neuralgia refractory to other treatments, HIV neuropathy, and central post-stroke pain.

PMID: 12221151

Rating: 1b

Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998 Dec 2;280(21):1831-6.

CONCLUSION: 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.

PMID: 9846777

Rating: 2b

Bader S, Dürk T, Becker G. Methylnaltrexone for the treatment of opioid-induced constipation. *Expert Rev Gastroenterol Hepatol*. 2013 Jan;7(1):13-26. doi: 10.1586/egh.12.63.

PMID: 23265145

Rating: 5b

Baillargeon L, Landreville P, Verreault R, Beauchemin JP, Gregoire JP, Morin CM. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. *CMAJ*. 2003 Nov 11;169(10):1015-20.

INTERPRETATION: A combination of cognitive-behavioural therapy and benzodiazepine tapering was superior to tapering alone in the management of patients with insomnia and chronic benzodiazepine use.

PMID: 14609970

Rating: 2b

Bailey AM, Wermeling DP. Naloxone for opioid overdose prevention: pharmacists' role in community-based practice settings. Ann Pharmacother. 2014; 48:601-6.

PMID: 24523396

Rating: 11b

Bair MJ, Wu J, Damush TM, Sutherland JM, Kroenke K. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. *Psychosom Med*. 2008;70:890-7.

CONCLUSIONS: The added morbidity of depression and anxiety with chronic pain is strongly associated with more severe pain, greater disability, and poorer HRQL.

PMID: 18799425

Rating 3a

Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson JR, den Boer JA, Fineberg NA, Knapp M, Scott J, Wittchen HU; British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2005; 19:567-96.

PMID: 16272179

Rating: 5a

Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci*. 2008 Feb 6;28(6):1398-403.

Recent studies have demonstrated that chronic pain harms cortical areas unrelated to pain.

PMID: 18256259

Rating: 4c

Bandelow B, Zohar J, Hollander E, Kasper S, Möller HJ; World Federation of Societies of Biological Psychiatry Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Posttraumatic Stress Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders. *World J Biol Psychiatry*. 2002; 3:171-99

Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for panic disorder. Tri2-cyclic antidepressants (TCAs) are equally effective, but they are less well tolerated than the SSRIs..

PMID: 12516310

Rating: 5a

Bansal V, Kalita J, Misra UK. Diabetic neuropathy. *Postgrad Med J.* 2006 Feb;82(964):95-100.

For diagnosis of DN, symptoms, signs, quantitative sensory testing, nerve conduction study, and autonomic testing are used; and two of these five are recommended for clinical diagnosis.

PMID: 16461471

Rating: 5a

Baraf HS, Gloth FM, Barthel HR, Gold MS, Altman RD. Safety and efficacy of topical diclofenac sodium gel for knee osteoarthritis in elderly and younger patients: pooled data from three randomized, double-blind, parallel-group, placebo-controlled, multicentre trials. *Drugs Aging*. 2011 Jan 1;28(1):27-40.

RESULTS: The MES included both patients aged 25-64 (n = 602) and ≥65 (n = 374) years. Treatment-related application site dermatitis was more common with DSG. Gastrointestinal AEs were infrequent.

PMID: 21174485

Rating: 2b

Barbaud A. Contact dermatitis due to topical drugs. *G Ital Dermatol Venereol*. 2009;144:527-36.

In case of photosensitization 1) to ketoprofen or 2) piroxicam the topical and/or systemic administration of the following molecules are contraindicated with respectively 1) ketoprofen, tiaprofenic acid, fenofibrate, oxybenzone or 2) piroxicam, thimerosal.

PMID: 19834431

Rating: 5b

Barbui C, Guaiana G, Hotopf M. Amitriptyline for inpatients and SSRIs for outpatients with depression? Systematic review and meta-regression analysis. *Pharmacopsychiatry.* 2004 May;37(3):93-7.

CONCLUSIONS: These data suggest that a reasonable approach could be the first-line prescription of newer agents in the routine outpatient care of depressive subjects, and the use of amitriptyline in inpatients with severe depression.

PMID: 15179966

Rating: 1a

Barrows KA, Jacobs BP. Mind-body medicine. An introduction and review of the literature. *Medical Clinics of North America.* 01-Jan-2002; 86(1): 11-31.

MBM therapies are effective in improving quality of life, anxiety, and pain intensity for a variety of conditions.

PMID: 11795084

Bart G. Maintenance medication for opiate addiction: the foundation of recovery. *J Addict Dis.* 2012;31(3):207-25

PMID: 22873183

Rating: 5b

Bartels S, Sivilotti M, Crosby D, Richard J. Are recommended doses of acetaminophen hepatotoxic for recently abstinent alcoholics? A randomized trial. *Clin Toxicol (Phila).* 2008;46:243-9.

PMID: 18344107

Rating: 2b

Beals RK, Hickman NW. Industrial injuries of the back and extremities. Comprehensive evaluation--an aid in prognosis and management: a study of one hundred and eighty patients. *J Bone Joint Surg Am.* 1972;54:1593-611.

PMID: 4143913

Rating: 3b

Beerthuizen A, van 't Spijker A, Huygen FJ, Klein J, de Wit R. Is there an association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1) in adults? A systematic review. *Pain*. 2009;145:52-9.

PMID: 19573987

Rating: 1c

Beerthuizen A, Stronks DL, Huygen FJ, Passchier J, Klein J, Spijker AV. The association between psychological factors and the development of complex regional pain syndrome type 1 (CRPS1)--a prospective multicenter study. *Eur J Pain*. 2011;15:971-5.

PMID: 21459637

Rating: 3a

Beletsky L, Rich JD, Walley AY. Prevention of fatal opioid overdose. JAMA. Nov 14 2012; 308(18):1863-1864.

PMID: 23150005

Rating: 5a

Beletsky L. The Benefits and Potential Drawbacks in the Approval of EVZIO for Lay Reversal of Opioid Overdose. Am J Prev Med. 2015;48:357-359.

PMID: 25547930

Rating: 11a

Benca RM. Diagnosis and treatment of chronic insomnia: a review. *Psychiatr Serv*. 2005;56:332-43.

CONCLUSIONS: Insomnia is particularly challenging for clinicians because of the lack of guidelines and the small number of studies conducted in patient populations with behavioral and pharmacologic therapies. Current treatment options do not address the needs of difficult-to-treat patients with chronic insomnia, such as the elderly, and those with comorbid medical and psychiatric conditions.

PMID: 15746509

Rating: 1c

Bendix AF, Bendix T, Labriola M, Boekgaard P. Functional restoration for chronic low back pain. Two-year follow-up of two randomized clinical trials. *Spine*. 1998 Mar 15;23(6):717-25.

STUDY DESIGN: Two randomized, prospective clinical trials involving 238 chronic low back disability patients were carried out. Results at 2-year follow-up are presented. METHODS: Two hundred thirty-eight patients with chronic low back disability of at least 6 months' duration were included. RESULTS: Of the remaining 225 patients, 20 (9%) did not complete treatment. The questionnaire response rate was 94%. In Project A, those patients receiving treatment (functional restoration) reported significantly less contact with the health care system, fewer sick leave days, and a less disabled life style during the follow-up period, compared with reports of patients in the control group. Other effect parameters did not demonstrate a significant difference between the two groups. CONCLUSIONS: indicate the necessity of testing a treatment program in different settings, in that the statistical variation may be a major factor in results of different studies.

PMID: 9549794

Rating: 2b

Bendix AF, Bendix T, Lund C, Kirkbak S, Ostenfeld S. Comparison of three intensive programs for chronic low back pain patients: a prospective, randomized, observer-blinded study with one-year follow-up. *Scand J Rehabil Med*. 1997;29:81-9.

Conclusively, it seems that there is human, as well as economical, benefit from a functional restoration program compared to less intensive programs for these patients.

PMID: 9198257

Rating: 2b

Bendix AF, Bendix T, Haestrup C. Can it be predicted which patients with chronic low back pain should be offered tertiary rehabilitation in a functional restoration program? A search for demographic, socioeconomic, and physical predictors. *Spine*. 1998;23:1775-83; discussion 1783-4.

CONCLUSIONS: Different factors can be identified as predictive of outcome in a functional restoration program, but most of these factors were also shown to predict success for shorter control outpatient programs or of no treatment.

PMID: 9728378

Rating: 2b

Bendix T, Bendix A, Labriola M, Haestrup C, Ebbehøj N. Functional restoration versus outpatient physical training in chronic low back pain: a randomized comparative study. *Spine*. 2000;25:2494-500.

DISCUSSION: It may be that lower economic benefits during sick leave in the United States lead to favorable results from functional restoration programs, whereas greater benefits in Canada, Finland, and Denmark result in different conclusions.

PMID: 11013502

Rating: 2b

Bennett G, Burchiel K, Buchser E, Classen A, Deer T, Du Pen S, Ferrante FM, Hassenbusch SJ, Lou L, Maeyaert J, Penn R, Portenoy RK, Rauck R, Serafini M, Willis KD, Yaksh T. Clinical guidelines for intraspinal infusion: report of an expert panel. PolyAnalgesic Consensus Conference 2000. *J Pain Symptom Manage*. 2000 Aug;20(2):S37-43.

PMID: 10989256

Rating: 8b

Benzon HT, Raja SN, Molloy RE, Liu SS, Fishman SM. Essentials of Pain Medicine and Regional Anesthesia. 2nd ed. Elisevier 2005, p. 215.

Rating: 9a

Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. *Pain Med*. 2006 Jan-Feb;7(1):25-9.

In this article, we review our clinical experience of 20 adult patients with chronic noncancer pain. Nabilone may be a useful addition to pain management and should be further evaluated in randomized controlled trials.

PMID: 16533193

Rating: 4b

Bernacki EJ, Guidera JA, Schaefer JA, Tsai S, A facilitated early return to work program at a large urban medical center, *J Occup Environ Med* 2000 Dec;42(12):1172-7

PMID: 11125680

Rating: 5a

Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, Bombardier C, Cannon C, Farkouh ME, FitzGerald GA, Goss P, Halls H, Hawk E, Hawkey C, Hennekens C, Hochberg M, Holland LE, Kearney PM, Laine L, Lanas A, Lance P, Laupacis A, Oates J, Patrono C, Schnitzer TJ, Solomon S, Tugwell P, Wilson K, Wittes J, Baigent C. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013 Aug 31;382(9894):769-79. doi: 10.1016/S0140-6736(13)60900-9.

PMID: 23726390

Rating: 1a

Bhattacharyya S, Crippa JA, Allen P, Martin-Santos R, Borgwardt S, Fusar-Poli P, Rubia K, Kambeitz J, O'Carroll C, Seal ML, Giampietro V, Brammer M, Zuardi AW, Atakan Z, McGuire PK. Induction of psychosis by {delta}9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. *Arch Gen Psychiatry*. 2012 Jan;69(1):27-36.

Δ9-Tetrahydrocannabinol and CBD differentially modulate prefrontal, striatal, and hippocampal function during attentional salience processing. These effects may contribute to the effects of cannabis on psychotic symptoms and on the risk of psychotic disorders.

PMID: 22213786

Rating: 3c

Bigos SJ, McKee JE, Holland JP, Holland CL, Hildebrandt J, Back pain, the uncomfortable truth - assurance and activity problem. Schmerz 2001 Dec;15(6):430-4

PMID: 11793147

Rating: 5a

Birklein F. Complex regional pain syndrome. *J Neurol*. 2005 Feb;252(2):131-8.

PMID: 15729516

Rating: 5b

Biswal S, Medhi B, Pandhi P. Longterm efficacy of topical nonsteroidal antiinflammatory drugs in knee osteoarthritis: metaanalysis of randomized placebo controlled clinical trials. *J Rheumatol*. 2006;33:1841-4.

CONCLUSION: Topical NSAID are effective for pain relief in knee OA for a longer duration; however, this may not hold true for all the preparations.

PMID: 16960944

Rating: 1c

Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. *Eur J Pain.* 2007;11:125-38.

Heterogeneity tests revealed that best efficacy values of topical NSAIDs may be slightly deflated, while data for oral NSAIDs may be slightly inflated due to probable patient selection bias.

PMID: 16682240

Rating 1c

Blommel ML, Blommel AL. Pregabalin: an antiepileptic agent useful for neuropathic pain. *Am J Health Syst Pharm*. 2007;15;64:1475-82.

Pregabalin may be beneficial for the treatment of neuropathic pain or partial-onset seizures in patients who do not respond to conventional treatments or cannot tolerate their adverse effects.

PMID: 17617497

Rating: 5b

BlueCross BlueShield, Surgery Section - Percutaneous Electrical Nerve Stimulation (PENS), Policy No: 44, 08/03/2004

Rating: 8b

BlueCross BlueShield, Durable Medical Equipment Section - Electrical Stimulation Devices for Home Use, DME Policy No: 11, Approved Date: 04/05/2005. Also Electrical Stimulators for pain, seizures, or cerebral palsy. Policy 003; Posted 4/23/07.

Rating: 8b

BlueCross BlueShield, Durable Medical Equipment Section - Sympathetic Therapy for the Treatment of Pain, DME Policy No: 65. Effective Date: 03/01/2005

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.

Rating: 8b

BlueCross BlueShield, Durable Medical Equipment Section - Interferential Stimulation, DME Policy No: 66. Effective Date: 03/01/2005. Updated 2006.

Interferential current stimulation is considered investigational. The results of placebo-controlled trials have reported negative findings of interferential therapy. Interferential therapy (such as RS-4i): Is denied experimental/investigational.

Rating: 8b

BlueCross BlueShield, Durable Medical Equipment Section - Biomagnetic Therapy, DME Policy No: 55, Effective Date: 03/01/2005

The data from the above randomized, placebo-controlled clinical trials fails to demonstrate that biomagnetic therapy results in improved health outcomes for any type of pain.

Rating: 8b

BlueCross BlueShield. Surgery Section - Fully Implantable Infusion Pump. Policy No: 18. Effective Date: 04/05/2005

Fully implantable infusion pumps are considered investigational for all other indications.

Rating: 8c

BlueCross BlueShield. Medicine Section - Low Level Laser Treatment of Neuromuscular Pain Disorders. Policy No: 105, Effective Date: 03/01/2005

Rating: 8b

BlueCross BlueShield. Utilization Management Section - Pain Rehabilitation Programs. Policy No: 5, Effective Date: 06/01/2004

Rating: 8b

BlueCross BlueShield. Surgery Section - Spinal Cord Stimulation for Treatment of Pain. Policy No: 45, Effective Date: 07/06/2004

Rating: 8b

BlueCross BlueShield. Allied Health - Biofeedback as a Treatment of Chronic Pain. Policy No: 28. Effective Date: 08/03/2004

The available evidence did not clearly show whether biofeedback's effects exceeded nonspecific placebo effects. It was also unclear whether biofeedback added to the effectiveness of relaxation training alone.

Rating: 8b

References

1. BlueCross BlueShield Association Medical Policy Reference Manual; Policy No. 2.01.30
2. NIH Technology Assessment Panel. Integration of behavioral and relaxation approaches into the treatment of chronic pain and insomnia. NIH Technology Assessment Panel on Integration of Behavioral and Relaxation Approaches into the Treatment of Chronic Pain and Insomnia. *JAMA* 1996;276(4):313-8
3. 1996 TEC Assessment: Biofeedback
4. Bush C, Ditto B, Feuerstein M. A controlled evaluation of paraspinal EMG biofeedback in the treatment of chronic low back pain. *Health Psychol* 1985;4(4):307-21
5. Stuckey SJ, Jacobs A, Goldfarb J. EMG biofeedback training, relaxation training, and placebo for the relief of chronic back pain. *Percept Mot Skills* 1986;63(3):1023-36
6. Flor H, Haag G, Turk DC et al. Efficacy of EMG biofeedback, pseudotherapy, and conventional medical treatment for chronic rheumatic back pain. *Pain* 1983;17(1):21-31
7. Buckelew SP, Conway R, Parker J et al. Biofeedback/relaxation training and exercise interventions for fibromyalgia: a prospective trial. *Arthritis Care Res* 1998;11(3):196-209
8. Dursun N, Dursun E, Kilic Z. Electromyographic biofeedback-controlled exercise versus conservative care for patellofemoral pain syndrome. *Arch Phys Med Rehabil* 2001; 82(12):1692-5
9. Humphreys PA, Gevirtz RN. Treatment of recurrent abdominal pain: components analysis of four treatment protocols. *J Pediatr Gastroenterol Nutr* 2000;31(1):47-51
10. Bergeron S, Binik YM, Khalife S et al. A randomized comparison of group cognitive-behavioral therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. *Pain* 2001;91(3):297-306
11. van Santen M, Bolwijn P, Verstappen F et al. A randomized clinical trial comparing fitness and biofeedback training versus basic treatment in patients with fibromyalgia. *J Rheumatol* 2002;29(3):575-81
12. Astin JA, Beckner W, Soeken K et al. Psychological interventions for rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis Rheum* 2002;47(3):291-302
13. Weydert JA, Ball TM, Davis MF. Systematic review of treatments for recurrent abdominal pain. *Pediatrics* 2003; 111(1):e1-11

BlueCross BlueShield. Medicine Section - Trigger Point Therapy. Policy No: 39. Effective Date: 11/01/2004

Rating: 8c

BlueCross BlueShield. Medicine Section - Prolotherapy. Policy No: 40. Effective Date: 07/11/06

Rating: 8b

BlueCross BlueShield. Radiology Section - Thermography. Policy No: 17. Effective Date: 04/05/2005

Rating: 8b

BlueCross. Pulsed Radiofrequency (PRF) Treatment for Chronic Pain Syndromes. Policy #: MED.00071. Current Effective Date: 09/22/2005

Rating: 8c

BlueCross of California. Implantable Infusion Pumps. Policy #: SURG.00068. Current Effective Date: 07/14/2005

Rating: 8a

Blum K, Chen TJ, Martinez-Pons M, Dinubile NA, Waite RL, Schoolfield J, Blum SH, Mengucci J, Downs BW, Meshkin B. The H-Wave small muscle fiber stimulator, a nonpharmacologic alternative for the treatment of chronic soft-tissue injury and neuropathic pain: an extended population observational study. *Adv Ther*. 2006 Sep-Oct;23(5):739-49.

PMID: 17142209

Rating: 4c

Patient Selection Criteria from the study: All enrolled patients had a previous 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, such as physical therapy, medications, and transcutaneous electrical nerve stimulation (TENS), and other analgesic electrical stimulator modalities.

Blum K, DiNubile NA, Tekten T, Chen TJ, Waite RL, Schoolfield J, Martinez-Pons M, Callahan MF, Smith TL, Mengucci J, Blum SH, Meshkin B. H-Wave, a nonpharmacologic alternative for the treatment of patients with chronic soft tissue inflammation and neuropathic pain: a preliminary statistical outcome study. *Adv Ther*. 2006 May-Jun;23(3):446-55.

PMID: 16912027

Rating: 4c

Blum K, Chen AL, Chen TJ, Prihoda TJ, Schoolfield J, Dinubile N, Waite RL, Arcuri V, Kerner M, Braverman ER, Rhoades P, Tung H. The H-Wave(R) device is an effective and safe non-pharmacological analgesic for chronic pain: a meta-analysis. *Adv Ther.* 2008 Jul;25(7):644-57.

PMID: 18636234

Rating: 1c

Note: 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. For reported results concerning "Reduction in pain medication" and "Increased functionality," the meta-analysis relied 100% on the Blum 2006 studies. For reported results concerning "Reduction in pain," there were 4 studies, with 3 small prospective studies that looked only at diabetic neuropathy, plus the Blum 2006 study, but the Blum study accounted for 92% of the effect size sample for this measurement. The study also says, “RCTs were found to have a signifcantly lower effect size.” The Blum 2006 studies that dominate this meta-analysis were retrospective observational studies using a patient survey, the H-Wave Customer Service Questionnaire, without a prospective control group. According to this meta-analysis, "double-blinded studies of the H-Wave device are currently underway and results will be awaited with interest." The study author is an outside independent consultant of Electronic Waveform Lab, Inc.

Blum K, Chen AL, Chen TJ, Waite RL, Downs BW, Braverman ER, Kerner MM, Savarimuthu SM, DiNubile N. Repetitive H-wave device stimulation and program induces significant increases in the range of motion of post operative rotator cuff reconstruction in a double-blinded randomized placebo controlled human study. *BMC Musculoskelet Disord*. 2009 Oct 29;10:132. doi: 10.1186/1471-2474-10-132.

PMID: 19874593

Rating: 2c

Bocanegra TS, Weaver AL, Tindall EA, Sikes DH, Ball JA, Wallemark CB, Geis GS, Fort JG. Diclofenac/misoprostol compared with diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized, placebo controlled trial. Arthrotec Osteoarthritis Study Group. *J Rheumatol.* 1998;25:1602-11.

CONCLUSION: Diclofenac 50 mg/misoprostol 200 microg t.i.d. and diclofenac 75 mg/misoprostol 200 microg b.i.d. are as efficacious as diclofenac 75 mg b.i.d. in the treatment of OA, but are associated with a significantly lower incidence of gastric and/or duodenal ulcers.

PMID: 9712107

Rating: 2a

Bolona ER, Uraga MV, Haddad RM, Tracz MJ, Sideras K, Kennedy CC, Caples SM, Erwin PJ, Montori VM. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc*. 2007;82:20-8.

Testosterone use in men is associated with small improvements in satisfaction with erectile function and moderate improvements in libido. Unexplained inconsistent results across trials, wide CIs, and possible reporting bias weaken these inferences.

PMID: 17285782

Rating: 1a

Boothby LA, Doering PL, Halton RC. Carisoprodol: A marginally effective skeletal muscle relaxant with serious abuse potential. *Hospital Pharmacy*. 2003;38:337-45.

Rating: 9b

Borchers AT, Gershwin ME. Complex regional pain syndrome: A comprehensive and critical review. *Autoimmun Rev*. 2013 Oct 23. pii: S1568-9972(13)00181-X. doi: 10.1016/j.autrev.2013.10.006.

PMID: 24161450

Rating: 5a

Borg-Stein J, Simons DG. Focused review: myofascial pain. *Arch Phys Med Rehabil*. 2002 Mar;83(3 Suppl 1):S40-7, S48-9.

PMID: 11973695

Rating: 5a

Borsook D, Becerra LR. Breaking down the barriers: fMRI applications in pain, analgesia and analgesics. *Mol Pain*. 2006 Sep 18;2:30.

PMID: 16982005

Rating: 5b

Borsook, D., et al. Neuroimaging revolutionizes therapeutic approaches to chronic pain. *Molecular Pain*. 2000; Volume 3, Number 25.

PMID: 17848191

Rating: 5c

Quality: N/A. Total Rating: N/A. Comment: Does not meet inclusion criteria for evidence-based review.

Boseman J, Disability management. Application of a nurse based model in a large corporation, *AAOHN J* 2001 Apr;49(4):176-86

PMID: 11760522

Rating: 5b

Boswell MV, Shah RV, Everett CR, Sehgal N, Mckenzie-Brown AM, Abdi S, Bowman RC, Deer TR, Datta S, Colson JD, Spillane WF, Smith HS, Lucas LF, Burton AW, Chopra P, Staats PS, Wasserman RA, Manchikanti L. Interventional Techniques in The Management of Chronic Spinal Pain: Evidence-Based Practice Guidelines. *Pain Physician*. 2005;8:1-47

[Note: Much of the evidence used in this practice guideline for pain physicians is based on studies published in *Pain Physician*, a journal not included in Medline's list of indexed journals evaluated for quality that offer the credibility of an independent peer-review process. These studies were not part of the evidence base for *ODG Treatment* or the *ACOEM Guidelines*.]

Rating: 6c

Boswell MV, Trescot AM, Datta S, Schultz DM, Hansen HC, Abdi S, Sehgal N, Shah RV, Singh V, Benyamin RM, Patel VB, Buenaventura RM, Colson JD, Cordner HJ, Epter RS, Jasper JF, Dunbar EE, Atluri SL, Bowman RC, Deer TR, Swicegood JR, Staats PS, Smith HS, Burton AW, Kloth DS, Giordano J, Manchikanti L. Interventional Techniques: Evidence-based Practice Guidelines in the Management of Chronic Spinal Pain. *Pain Physician*. 2007;10:7-111.

These guidelines also do not represent a “standard of care.”

Rating: 6b

Boyer EW. Management of opioid analgesic overdose. N Engl J Med. 2012;367:146-55.

PMID: 22784117

Rating: 5a

Braham R, Dawson B, Goodman C, The effect of glucosamine supplementation on people experiencing regular knee pain, *Br J Sports Med*. 2003 Feb;37(1):45-9; discussion 49

PMID: 12547742

Rating: 2b

Bramness JG, Skurtveit S, Mørland J, Engeland A. The risk of traffic accidents after prescriptions of carisoprodol. *Accid Anal Prev*. 2007;39:1050-5.

PMID: 17854578

Rating: 3a

Bramness JG, Skurtveit S, Mørland J. Impairment due to intake of carisoprodol. *Drug Alcohol Depend*. 2004;74:311-8.

PMID: 15194209

Rating: 4b

Brason FW 2nd, Roe C, Dasgupta N. Project Lazarus: an innovative community response to prescription drug overdose. N C Med J. 2013;74:259-61.

PMID: 23940903

Rating: 5b

Breit R, Van der Wall H. Transcutaneous electrical nerve stimulation for postoperative pain relief after total knee arthroplasty. *J Arthroplasty*. 2004 Jan;19(1):45-8.

We conclude that there is no utility for TENS in the postoperative management of pain after knee arthroplasty.

PMID: 14716650

Rating 2c

Broomhead A, Kerr R, Tester W, O'Meara P, Maccarrone C, Bowles R, Hodsman P. Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for cancer pain. *J Pain Symptom Manage*. 1997;14:63-73.

PMID: 9262035

Rating: 1c

Brosseau L, Welch V, Wells G, DeBie R, Gam A, Harman K, Morin M, Shea B, Tugwell P, Low level laser therapy (Classes I, II and III) for treating osteoarthritis, *Cochrane Database Syst Rev.* 2004;(3):CD002046

CONCLUSIONS: For OA, the results are conflicting in different studies and may depend on the method of application and other features of the LLLT application.

PMID: 15266461

Rating: 1b

Brown JE, Chatterjee N, Younger J, Mackey S. Towards a Physiology-Based Measure of Pain: Patterns of Human Brain Activity Distinguish Painful from Non-Painful Thermal Stimulation. *PLoS ONE* 6(9): e24124. Sept. 13, 2011.

In fMRI experiments, 24 individuals were presented painful and nonpainful thermal stimuli. Our findings demonstrate that fMRI with SVM learning can assess pain without requiring any communication from the person being tested.

Rating: 3c

Browning R, Jackson JL, O'Malley PG, Cyclobenzaprine and back pain: a meta-analysis, *Arch Intern Med.* 2001 Jul 9;161(13):1613-20.

CONCLUSIONS: Cyclobenzaprine 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.

PMID: 11434793

Rating: 1a

Bruce B, Fries J, Lubeck D. Aerobic exercise and its impact on musculoskeletal pain in older adults: a 14 year prospective, longitudinal study. Arthritis Res Ther 2005 Sept 19; R1263-R1270

Exercise was associated with significantly lower pain scores over time in the Runners' Association group after adjusting for gender, baseline BMI, and study attrition ($p < 0.01$). Similar differences were observed for Ever-Runners versus Never-Runners. Consistent exercise patterns over the long-term in physically active seniors are associated with about 25% less musculoskeletal pain than reported by more sedentary controls, either by calendar year or by cumulative area-under-the-curve pain over average ages of 62 to 76 years.

PMID: 16277679

Rating: 3a

Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. *Pain.* 1999 May;81(1-2):147-54.

These results indicate that the current IASP criteria for CRPS have inadequate specificity and are likely to lead to overdiagnosis.

PMID: 10353502

Rating: 4b

Bruehl S. An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology*. 2010;113:713-25.

PMID: 20693883

Rating: 5b

Bruns D. Colorado Division of Workers' Compensation, Comprehensive Psychological Testing: Psychological Tests Commonly Used in the Assessment of Chronic Pain Patients. 2001

The following 26 tests are described and evaluated:

1) BHI™ 2 (Battery for Health Improvement – 2nd edition)
2) MBHI™ (Millon Behavioral Health Inventory) [Has been superceded by the MBMD. The updated version of the test, the MBMD, should be administered instead.]
3) MBMD™ (Millon Behavioral Medical Diagnostic)
4) PAB (Pain Assessment Battery)
5) MCMI-111™ (Millon Clinical Multiaxial Inventory, 3rd edition)
6) MMPI-2™ (Minnesota Inventory- 2nd edition ™)
7) PAI™ (Personality Assessment Inventory)
8) BBHI™ 2 (Brief Battery for Health Improvement – 2nd edition)
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)
18) SCL-90-R® (Symptom Checklist –90 Revised)
19) BDI ®–II (Beck Depression Inventory-2nd edition)
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)

Rating: 7a

Burch F, Codding C, Patel N, Sheldon E. Lidocaine patch 5% improves pain, stiffness, and physical function in osteoarthritis pain patients. A prospective, multicenter, open-label effectiveness trial. *Osteoarthritis Cartilage*. 2004;12:253-5.

PMID: 14972343

Rating: 4b

Burch FX, Tarro JN, Greenberg JJ, Carroll WJ. Evaluating the benefits of patterned stimulation in the treatment of osteoarthritis of the knee: a multi-center, randomized, single-blind, controlled study with an independent masked evaluator. *Osteoarthritis Cartilage*. 2008 Aug;16(8):865-72. Epub 2008 Feb 8.

OBJECTIVE: This study investigated the benefits of the combination of interferential (IF) and patterned muscle stimulation in the treatment of osteoarthritis (OA) of the knee.
CONCLUSIONS: In patients with OA of the knee, home-based patterned stimulation appears to be a promising therapy for relieving pain, decreasing stiffness, and increasing function.

PMID: 18262443

Rating: 2b

The device used to deliver the electrical stimulation was the RS-4i Stimulator (RS Medical, 14001 SE First Street, Vancouver, WA). Stimulators were pre-programmed to deliver either IF plus patterned muscle stimulation or low-current TENS treatment. The study assessed the benefits of a home-based electrostimulation treatment combining IF and patterned muscle stimulation in treatment of OA of the knee. Low-current TENS was applied as a control. Our results suggest that patterned stimulation has the potential to be a more effective treatment modality than conventional single-step TENS for OA of the knee.
Conflict of interest: This study was supported by industrial funding. The sponsoring organization, RS Medical, has financial interest in patterned stimulation supplied by the RS-4i electrostimulation device. The corresponding author, WJ Carroll, is employed by the sponsor as Vice President of Research and Product Development. J.J. Greenberg was employed by the sponsor as Research Scientist during the conduct of the study. F.X. Burch, M.D., of Radiant Research, San Antonio and J.N. Tarro, M.D., of Radiant Research, Portland were paid contributors (as principal investigators).
Role of the Funding Source: The sponsor of this study, RS Medical, designed the study and provided the infrastructure for collecting study data. RS Medical and its paid consultants analyzed and interpreted the data and prepared this manuscript. RS Medical is responsible for the decision to submit the manuscript for publication.

Burton AW, Interventional Therapies. In: Complex Regional Pain Syndrome: Treatment Guidelines. Ed. Harden N. Reflex Sympathetic Dystrophy Syndrome Association. 2006.

No abstract available. A discussion of the role of interventional therapy for CRPS.

Rating: 5a

Buchner M, Zahlten-Hinguranage A, Schiltenwolf M, Neubauer E. Therapy outcome after multidisciplinary treatment for chronic neck and chronic low back pain: a prospective clinical study in 365 patients. *Scand J Rheumatol.* 2006 Sep-Oct;35(5):363-7.

CONCLUSION: Evaluation of the main results of this study suggests that patients with chronic NP also derive significant benefit from a multidisciplinary treatment strategy, demonstrated in the literature so far mainly for patients with chronic LBP.

PMID: 17062436

Rating: 3a

Burleson AM. American Academy of Pain Medicine 24th Annual Meeting (Orlando, FL): Abstract 105. February 15, 2008.

Physical conditioning in chronic pain patients can have immediate and long-term benefits, according to a new study presented at the American Academy of Pain Medicine 24th Annual Meeting. The final sample of 28 patients.

Rating: 10b

Buscemi N, Vandermeer B, Friesen C et al. Manifestations and Management of Chronic Insomnia in Adults. Summary,Evidence Report/Technology Assessment No. 125. (Prepared by the University of Alberta Evidence-based Practice Center, under Contract No. C400000021.) AHRQ Publication No.05-E021-1. Rockville, MD: Agency for Healthcare Research and Quality. June 2005. Archived at http://www.ncbi.nlm.nih.gov/books/NBK11906/

Rating 1 a

Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, Klassen TP, Witmans M. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med.* 2007;22:1335-50.

BACKGROUND: Hypnotics have a role in the management of acute insomnia; however, the efficacy and safety of pharmacological interventions in the management of chronic insomnia is unclear. CONCLUSIONS: Benzodiazepines and non-benzodiazepines are effective treatments in the management of chronic insomnia, although they pose a risk of harm. There is also some evidence that antidepressants are effective and that they pose a risk of harm.

PMID: 17619935

Rating: 1a

Busch AJ, Barber KA, Overend TJ, Peloso PM, Schachter CL. Exercise for treating fibromyalgia syndrome. *Cochrane Database Syst Rev*. 2007 Oct 17;(4):CD003786.

CONCLUSIONS: There is 'gold' level evidence (www.cochranemsk.org) that supervised aerobic exercise training has beneficial effects on physical capacity and FMS symptoms. Strength training may also have benefits on some FMS symptoms.

PMID: 17943797

Rating: 1b

Bush C, Ditto B, Feuerstein M. A controlled evaluation of paraspinal EMG biofeedback in the treatment of chronic low back pain. *Health Psychol.* 1985;4(4):307-21.

PMID: 2932330

Rating: 2b

Büssing A, Ostermann T, Lüdtke R, Michalsen A. Effects of yoga interventions on pain and pain-associated disability: a meta-analysis. *J Pain.* 2012 Jan;13(1):1-9.

This meta-analysis suggests that yoga is a useful supplementary approach with moderate effect sizes on pain and associated disability.

PMID: 22178433

Rating: 1b

Buvanendran A, Kroin JS. Useful adjuvants for postoperative pain management. *Best Pract Res Clin Anaesthesiol.* 2007 Mar;21(1):31-49.

Gabapentin-like compounds have low potency against acute pain, but in combination with opioids allow a reduction in opioid dose with improved analgesia.

PMID: 17489218

Rating: 5b

Buynak R, Shapiro DY, Okamoto A, Van Hove I, Rauschkolb C, Steup A, Lange B, Lange C, Etropolski M. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother.* 2010 Aug;11(11):1787-804.

DESIGN: Patients (N = 981) were randomized. CONCLUSIONS: Tapentadol ER effectively relieved moderate to severe chronic low back pain over 15 weeks and had better gastrointestinal tolerability than oxycodone.

PMID: 20578811

Rating: 2a

Calandre EP, Morillas-Arques P, Molina-Barea R, Rodriguez-Lopez CM, Rico-Villademoros F. Trazodone plus pregabalin combination in the treatment of fibromyalgia: a two-phase, 24-week, open-label uncontrolled study. *BMC Musculoskelet Disord*. 2011 May 16;12:95.

CONCLUSIONS: Trazodone significantly improved fibromyalgia severity and associated symptomatology. with pregabalin potentiated this improvement and the tolerability of the drugs in association was good.

PMID: 21575194

Rating: 3b

Caldwell JR. Avinza - 24-h sustained-release oral morphine therapy. Expert *Opin Pharmacother*. 2004;5:469-72

PMID: 14996642

Rating: 5c

California Technology Assessment Forum. Interferential stimulation for the treatment of musculoskeletal pain. 2005.

Interferential stimulation: Does Not Meet CTAF Criteria

Note: Click on link above to go to a description of each individual study.

Hou CR, Tsai LC, Cheng KF, Chung KC, Hong CZ. Immediate effects of various physical therapeutic modalities on cervical myofascial pain and trigger-point sensitivity. Arch Phys Med Rehabil. Oct 2002;83(10):1406-1414.
Hurley DA, McDonough SM, Dempster M, Moore AP, Baxter GD. A randomized clinical trial of manipulative therapy and interferential therapy for acute low back pain. Spine. Oct 15 2004;29(20):2207-2216.
Hurley DA, Minder PM, McDonough SM, Walsh DM, Moore AP, Baxter DG. Interferential therapy electrode placement technique in acute low back pain: a preliminary investigation. Arch Phys Med Rehabil. Apr 2001;82(4):485-493.
Jarit GJ, Mohr KJ, Waller R, Glousman RE. The effects of home interferential therapy on post-operative pain, edema, and range of motion of the knee. Clin J Sport Med. Jan 2003;13(1):16-20.
Werners R, Pynsent PB, Bulstrode CJ. Randomized trial comparing interferential therapy with motorized lumbar traction and massage in the management of low back pain in a primary care setting. Spine. Aug 1 1999;24(15):1579-1584.

Rating: 8b

California. Division of Workers' Compensation. Functional Improvement Report. October 2007.

§ 9792.27. Form FIR "Functional Improvement Report"

Rating: 7a

Cappello ZJ, Kasdan ML, Louis DS. Meta-analysis of imaging techniques for the diagnosis of complex regional pain syndrome type I. *J Hand Surg Am*. 2012;37:288-96.

PMID: 22177715

Rating: 1c

Carroll D, Moore RA, McQuay HJ, Fairman F, Tramer M, Leijon G, Transcutaneous electrical nerve stimulation (TENS) for chronic pain, *Cochrane Database Syst Rev.* 2001;(3):CD003222.

PMID: 11687055

Rating: 1a

Carson JW, Carson KM, Jones KD, Bennett RM, Wright CL, Mist SD. A pilot randomized controlled trial of the Yoga of Awareness program in the management of fibromyalgia. *Pain*. 2010 Nov;151(2):530-9.

A sample of 53 female FM patients were randomized to the 8-week Yoga of Awareness program. At post-treatment, women assigned to the yoga program showed significantly greater improvements.

PMID: 20946990

Rating: 2b

Centers for Disease Control and Prevention (CDC). CDC Grand Rounds: Prescription Drug Overdoses - a U.S. Epidemic. MMWR Morb Mortal Wkly Rep. 2012 Jan 13;61:10-3.

Rating: 3a

Center for Substance Abuse Treatment (2009). Emerging Issues in the Use of Methadone. HHS Publication No. (SMA) 09-4368. *Substance Abuse Treatment Advisory,* Volume 8, Issue 1.

Rating: 8b

Cepeda M, Carr D, Lau J. Local anesthetic sympathetic blockade for complex regional pain syndrome. *Cochrane Database Syst Rev*. 2005 Oct 19;4:CD004598.

RESULTS: Two small randomized double blind cross over studies that evaluated 23 subjects were found. CONCLUSIONS: This systematic review revealed the scarcity of published evidence to support the use of local anesthetic sympathetic blockade as the 'gold standard' treatment for CRPS.

PMID: 16235369

Rating: 1c

Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. *Cochrane Database Syst Rev*. 2006 ;19;3:CD005522.

CONCLUSIONS: Tramadol or tramadol/paracetamol decreases pain intensity, produces symptom relief and improves function, but these benefits are small. Adverse events, although reversible and not life threatening, often cause participants to stop taking the medication and could limit tramadol or tramadol plus paracetamol usefulness.

PMID: 16856101

Rating: 1a

Cepeda MS, Lau J, Carr DB. Defining the therapeutic role of local anesthetic sympathetic blockade in complex regional pain syndrome: a narrative and systematic review. *Clin J Pain.* 2002;18:216-33.

CONCLUSIONS: This review raises questions as to the efficacy of local anesthetic sympathetic blockade as treatment of CRPS. Its efficacy is based mainly on case series. Less than one third of patients obtained full pain relief. The absence of control groups in case series leads to an overestimation of the treatment response that can explain the findings.

PMID: 12131063

Rating: 1c

CFSAN/Office of Nutritional Products, Labeling, and Dietary Supplements. Guidance for Industry: Frequently Asked Questions About Medical Foods. Center for Food and Safety and Applied Nutrition, FDA. Accessed: July 2008

Rating: 8b

Chan FK, Graham DY. Review article: prevention of non-steroidal anti-inflammatory drug gastrointestinal complications--review and recommendations based on risk assessment. *Aliment Pharmacol Ther*. 2004;19:1051-61.

The presence of H. pylori infection increases the risk of upper gastrointestinal complications in non-steroidal anti-inflammatory drug users by two- to fourfold suggesting that all patients requiring regular non-steroidal anti-inflammatory drug therapy be tested for H. pylori.

PMID: 15142194

Rating: 5b

Chan AT, Manson JE, Albert CM, Chae CU, Rexrode KM, Curhan GC, Rimm EB, Willett WC, Fuchs CS. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation*. 2006;113:1578-87.

CONCLUSIONS: Use of NSAIDs or acetaminophen at high frequency or dose is associated with a significantly increased risk for major cardiovascular events, although more moderate use did not confer substantial risk.

PMID: 16534006

Rating: 3a

Chan FK, To KF, Wu JC, Yung MY, Leung WK, Kwok T, Hui Y, Chan HL, Chan CS, Hui E, Woo J, Sung JJ. Eradication of Helicobacter pylori and risk of peptic ulcers in patients starting long-term treatment with non-steroidal anti-inflammatory drugs: a randomised trial*. Lancet*. 2002;359:9-13.

INTERPRETATION: Screening and treatment for H pylori infection significantly reduces the risk of ulcers for patients starting long-term NSAID treatment.

PMID: 11809180

Rating: 2b

Chan FK, Chung SC, Suen BY, Lee YT, Leung WK, Leung VK, Wu JC, Lau JY, Hui Y, Lai MS, Chan HL, Sung JJ. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. *N Engl J Med*. 2001;344:967-73.

CONCLUSIONS: Omeprazole is superior to the eradication of H. pylori in preventing recurrent bleeding in patients who are taking other NSAIDs.

PMID: 11274623

Rating: 2b

Chang AK. Hydrocodone/Acetaminophen Not Superior to Codeine/Acetaminophen for Acute Pain. American Academy of Pain Medicine (AAPM) 30th Annual Meeting. Abstract 163. Presented March 8, 2014.

Rating: 10b

Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, Taylor RS. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess*. 2008 Apr;12(11):1-178.

CONCLUSIONS: With reduced costs of PPIs, future primary research needs to compare the effectiveness and cost-effectiveness of COX-2 selective NSAIDs relative to non-selective NSAIDs with a PPI.

PMID: 18405470

Rating: 1b

Chessick CA, Allen MH, Thase M, Batista Miralha da Cunha AB, Kapczinski FF, de Lima MS, dos Santos Souza JJ. Azapirones for generalized anxiety disorder. *Cochrane Database Syst Rev*. 2006; 3: CD006115.

CONCLUSIONS: Azapirones appeared to be useful in the treatment of GAD, particularly for those participants who had not been on a benzodiazepine. Azapirones may not be superior to benzodiazepines and do not appear as acceptable as benzodiazepines.

PMID: 16856115

Rating: 1c

Choi HK, Seeger JD, Kuntz KM, Effects of rofecoxib and naproxen on life expectancy among patients with rheumatoid arthritis: a decision analysis, *Am J Med*. 2004 May 1;116(9):621-9.

CONCLUSION: Our analysis suggests that the competing risks of upper gastrointestinal toxicity and myocardial infarction shown in the VIGOR trial would project a longer life expectancy with naproxen than rofecoxib among patients with rheumatoid arthritis, except in those at low risk of myocardial infarction or at high risk of upper gastrointestinal toxicity.

PMID: 15093759

Rating: 1b

Chong MS, Bajwa ZH. Diagnosis and treatment of neuropathic pain. *J Pain Symptom Manage.* 2003 May;25(5 Suppl):S4-S11.

PMID: 12694987

Rating: 5c

Chou R, Helfand M, Peterson K, Dana T, Roberts C. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis. Comparative Effectiveness Review No. 4. (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-02-0024.) Rockville, MD: Agency for Healthcare Research and Quality. September 2006.

Each of the analgesics evaluated in this report was associated with a unique set of benefits and risks. At this time, although the amount and quality of evidence vary, no currently available analgesic reviewed in this report was identified as offering a clear overall advantage compared with the others.

Rating: 1a

Table 18. Relative Risk (95% CI) of Upper GI tract bleeding/perforation for NSAIDs vs. non-use: Diclofenac 3.3; Ibuprofen 1.9; Indomethacin 4.6; Ketoprofen 4.6; Naproxen 4.0; Piroxicam 6.3; Sulindac 3.6.
http://www.effectivehealthcare.ahrq.gov/ehc/products/2/65/AnalgesicsFinal.pdf#page=66

Table 21. Risk of myocardial infarction associated with non-selective, non-naproxen NSAIDs: Ibuprofen 1.06; Diclofenac 1.18; Ketoprofen 1.08; Piroxicam 1.25; Indomethacin 0.86.
http://www.effectivehealthcare.ahrq.gov/ehc/products/2/65/AnalgesicsFinal.pdf#page=69

Rating: 1b

Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. *J Pain Symptom Manage*. 2004;28:140-75.

There is fair evidence that although the overall rate of adverse effects between tizanidine and baclofen is similar, tizanidine is associated with more dry mouth and baclofen with more weakness. There is fair evidence that cyclobenzaprine, carisoprodol, orphenadrine, and tizanidine are effective compared to placebo in patients with musculoskeletal conditions (primarily acute back or neck pain). Cyclobenzaprine has been evaluated in the most clinical trials and has consistently been found to be effective. There is very limited or inconsistent data regarding the effectiveness of metaxalone, methocarbamol, chlorzoxazone, baclofen, or dantrolene compared to placebo in patients with musculoskeletal conditions. There is insufficient evidence to determine the relative efficacy or safety of cyclobenzaprine, carisoprodol, orphenadrine, tizanidine, metaxalone, methocarbamol, and chlorzoxazone. Dantrolene, and to a lesser degree chlorzoxazone, have been associated with rare serious hepatotoxicity.

PMID: 15276195

Rating: 1a

Chu LF, D'Arcy N, Brady C, Zamora AK, Young CA, Kim JE, Clemenson AM, Angst MS, Clark JD. Analgesic tolerance without demonstrable opioid-induced hyperalgesia. *J Pain*. 2012 Aug;153(8):1583-92. doi: 10.1016/j.pain.2012.02.028. Epub 2012 Jun 16.

Patients with otherwise uncomplicated low-back pain were titrated to comfort or dose-limiting side effects in a prospective, randomized, double-blind, placebo-controlled clinical trial using sustained-release morphine or weight-matched placebo capsules for 1month. A total of 103 patients completed the study, with an average end titration dose of 78mgmorphine/d. After 1month, the morphine-treated patients developed tolerance to the analgesic effects of remifentanil, but did not develop opioid-induced hyperalgesia. On average, these patients experienced a 42% reduction in analgesic potency. The morphine-treated patients experienced clinically relevant improvements in pain relief, as shown by a 44% reduction in average visual analogue scale pain levels and a 31% improvement in functional ability. The differences in visual analogue scale pain levels (P=.003) and self-reported disability (P=.03) between both treatment groups were statistically significant. After 1 month of oral morphine therapy, patients with chronic low-back pain developed tolerance but not opioid-induced hyperalgesia. Improvements in pain and functional ability were observed.

Rating: 2b

Chu PS, Ma WK, Wong SC, Chu RW, Cheng CH, Wong S, Tse JM, Lau FL, Yiu MK, Man CW. The destruction of the lower urinary tract by ketamine abuse: a new syndrome? *BJU Int*. 2008 Dec;102(11):1616-22. Epub 2008 Aug 1.

CONCLUSION: A syndrome of cystitis and contracted bladder can be associated with street-ketamine abuse. Secondary renal damage can occur in severe cases which might be irreversible, rendering patients dependent on dialysis.

PMID: 18680495

Rating: 5b

Clark RE, Samnaliev M, Baxter JD, Leung GY. The Evidence Doesn't Justify Steps By State Medicaid Programs To Restrict Opioid Addiction Treatment With Buprenorphine. *Health Aff (Millwood).* 2011 Aug;30(8):1425-33.

We compared spending, the use of services related to drug-use relapses, and mortality for 33,923 beneficiaries. The evidence does not support rationing buprenorphine to save money or ensure safety.

PMID: 21821560

Rating: 3a

Clay FJ, Newstead SV, Watson WL, Ozanne-Smith J, Guy J, McClure RJ. Bio-psychosocial determinants of persistent pain 6 months after non-life-threatening acute orthopaedic trauma. *J Pain*. 2010 May;11(5):420-30.

Psychosocial factors strongly predicted persistent pain, pain-related work disability, and pain severity.

PMID: 20439055

Rating: 3b

Climent JM, Kuan TS, Fenollosa P, Martin-Del-Rosario F. Botulinum toxin for the treatment of myofascial pain syndromes involving the neck and back: a review from a clinical perspective. *Evid Based Complement Alternat Med*. 2013;2013:381459. doi: 10.1155/2013/381459.

PMID: 23533477

Rating: 1b

***Clinical Pharmacology*. Gold Standard Inc. Tampa, FL. 2008-2014.**

Rating: 9a

Cluver JS, Wright TM, Myrick H. Pharmacologic interventions for sedative-hypnotic addiction. In Reis RK, Fiellin DA, Miller SC, Saitz R. eds. *Principles of Addiction Medicine*, 4th edition. Lippincott Williams & Wilkins, 2009.

Rating: 9a

CMS, 2014. Clarification of the Confined to the Home Definition in Chapter 15, Covered Medical and Other Health Services, of the Medicare Benefit Policy Manual. Centers for Medicare and Medicaid (CMS), Pub.100-02, Transmittal: 192, August 1, 2014.

Rating: 8a

CMS, 2015. OASIS-C1/ICD-9 Guidance Manual, Centers for Medicare and Medicaid Services, Chapter 1, January 1, 2015.

Rating: 8a

Coffey RJ, Owens ML, Broste SK, Dubois MY, Ferrante FM, Schultz DM, et al. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat non-cancer pain. *Anesthesiology* 2009;111(4):881-891.

CONCLUSIONS: Patients with noncancer pain treated with intrathecal opioid therapy experience increased mortality compared to similar patients treated by using other therapies.

PMID: 19774431

Rating: 4c

Coffin PO, Sullivan SD. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. Ann Intern Med. 2013;158:1-9.

PMID: 23277895

Rating: 3a

Cole AJ, Herring SA, eds. The low back pain handbook. 2nd ed. Philadelphia: Hanley & Belfus; 2003: page 362.

Rating: 9b

Collins SL, Moore RA, McQuayHJ, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. *J Pain Symptom Manage.* 2000 Dec;20(6):449-58.

There was no evidence that selective serotonin reuptake inhibitors (SSRIs) were better than older antidepressants, and no evidence that gabapentin was better than older anticonvulsants. In these trials patients were more likely to stop taking antidepressants than anticonvulsants because of adverse effects.

PMID: 11131263

Rating: 2b

Colombo B, Annovazzi PO, Comi G. Medications for neuropathic pain: current trends. *Neurol Sci.* 2006 May;27 Suppl 2:s183-9.

Therapy is based on tricyclic antidepressants and antiepileptic drugs, the most frequently studied drug classes. Opioids and analgesics are a second-line choice. Topical medications could be useful in several pain situations.

PMID: 16688627

Rating: 5b

Colson J, Helm S, Silverman SM. Office-based opioid dependence treatment. *Pain Physician*. 2012;15:ES231-6

Approval of buprenorphine and buprenorphine/ naloxone has revolutionized opioid dependence therapy.

PMID: 22786460

Rating: 5a

Conaghan PG, Dickson J, Grant RL; Guideline Development Group.Care and management of osteoarthritis in adults: summary of NICE guidance. *BMJ*. 2008;336:502-3.

Initial pharmacological treatment includes acetaminophen and topical NSAIDs.

PMID: 18310005

Rating: 8a

Condon JE, Borg-Stein J, Revord J et al. A multicenter trial of percutaneous neuromodulation therapy for low back pain patients with a subacute duration of lower extremity pan. Presented at the American Academy of Pain Medicine Annual Meeting. San Francisco, CA, March 1, 2002

This study was an uncontrolled case series of 83 patients with low back pain. While pain improved at 5-week follow-up, the lack of a control group precludes scientific assessment. These preliminary reports do not offer data on outcomes in pain management.

Rating: 10c

Cooper ZD, Comer SD, Haney M. Comparison of the Analgesic Effects of Dronabinol and Smoked Marijuana In Daily Marijuana Smokers. *Neuropsychopharmacology.* 2013 Apr 22. doi: 10.1038/npp.2013.97.

PMID: 23609132

Rating: 2c

Cooper MS, Clark VP. Neuroinflammation, neuroautoimmunity, and the co-morbidities of complex regional pain syndrome. *J Neuroimmune Pharmacol*. 2013;8:452-69.

PMID: 22923151

Rating: 5c

Corbin L. Safety and efficacy of massage therapy for patients with cancer. *Cancer Control*. 2005 Jul;12(3):158-64.

CONCLUSIONS: The strongest evidence for benefits of massage is for stress and anxiety reduction, although research for pain control and management of other symptoms common to patients with cancer, including pain, is promising. The oncologist should feel comfortable discussing massage therapy with patients and be able to refer patients to a qualified massage therapist as appropriate.

PMID: 16062163

Rating: 5b

Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Med. 2004 Sep;5(3):263-75.

CONCLUSION: This retrospective review suggests that limited subanesthetic inpatient infusions of 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 novel approach.

PMID: 15367304

Rating: 4b

Cowan P, Kelly N. Quality Of Life Scale, A Measure Of Function For People With Pain. The American Chronic Pain Association. 2008

The American Chronic Pain Association has developed a Quality of Life Scale. It is a self-assessment of function for people with pain.

Rating: 8b

Crane JD, Ogborn DI, Cupido C, Melov S, Hubbard A, Bourgeois JM, Tarnopolsky MA. Massage therapy attenuates inflammatory signaling after exercise-induced muscle damage. *Sci Transl Med.* 2012 Feb 1;4(119):119ra13.

In summary, when administered to skeletal muscle that has been acutely damaged through exercise, massage therapy appears to be clinically beneficial by reducing inflammation and promoting mitochondrial biogenesis.

PMID: 22301554

Rating: 3c

Crisostomo RA, Schmidt JE, Hooten WM, Kerkvliet JL, Townsend CO, Bruce BK. Withdrawal of analgesic medication for chronic low-back pain patients: improvement in outcomes of multidisciplinary rehabilitation regardless of surgical history. *Am J Phys Med Rehabil*. 2008;87:527-36.

CONCLUSIONS: Study results demonstrate that multidisciplinary pain rehabilitation treatment incorporating analgesic medication withdrawal is associated with significant clinical improvements in physical and emotional functioning, regardless of lumbar spine surgical history.

PMID: 18574345

Rating: 3c

Note: The CI of 1.0 for return to work indicates a trend only.

Croce RV. The effects of EMG biofeedback on strength acquisition. *Biofeedback Self Regul*. 1986 Dec;11(4):299-310.

Twenty-one male volunteers recruited from physical education classes at a large southwestern university were randomly assigned to one of the following three treatment groups: (1) a biofeedback (BF) trained group, (2) a deception (DEC) trained group, and (3) a nonfeedback (NF) trained group. Overall, these results were taken as supporting the hypothesis that a training program of combined isokinetics and EMG biofeedback produces significant gains in maximal force and IEMG activity of leg-extensor muscles.

PMID: 3607096

Rating: 2c

Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP Jr, LaMoreaux LK, Martin SA, Sharma U; Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2005;52:1264-73.

CONCLUSION: Pregabalin at 450 mg/day was efficacious for the treatment of FMS, reducing symptoms of pain, disturbed sleep, and fatigue compared with placebo. Pregabalin was well tolerated and improved global measures and health-related quality of life.

PMID: 15818684

Rating: 2b

Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, Daniell G, Heesakkers J, Haag-Molkenteller C. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. *Eur Urol*. 2011 Oct;60(4):742-50.

OnabotulinumtoxinA significantly reduced UI and improved urodynamics and QOL in MS and SCI patients with NDO.

PMID: 21798658

Rating: 2b

Cummings TM, White AR. Needling therapies in the management of myofascial trigger point pain: a systematic review. *Arch Phys Med Rehabil*. 2001;82:986-92.

PMID: 11441390

Rating: 1b

Daniell HW, Lentz R, Mazer NA. Open-label pilot study of testosterone patch therapy in men with opioid-induced androgen deficiency. *J Pain*. 2006;7:200-10.

PMID: 16516826

Rating: 4c

Daniels S, Casson E, Stegmann JU, Oh C, Okamoto A, Rauschkolb C, Upmalis D. A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin*. 2009 Jun;25(6):1551-61.

METHODS: Randomized patients (N = 901). CONCLUSIONS: Clinically meaningful and statistically significant improvements were observed with tapentadol IR 50 mg and 75 mg compared with placebo. Tapentadol IR 50 mg and 75 mg were non-inferior to oxycodone HCl IR 10 mg. The incidence of nausea and/or vomiting was statistically significantly lower for tapentadol IR 50 mg and numerically lower for tapentadol IR 75 mg than for oxycodone HCl IR 10 mg.

PMID: 19445652

Rating: 2b

Daniels SE, Upmalis D, Okamoto A, Lange C, Häeussler J. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. *Curr Med Res Opin*. 2009 Mar;25(3):765-76.

METHODS: Randomized patients (N = 603). CONCLUSIONS: Multiple doses of tapentadol IR (50, 75, and 100 mg) significantly relieve acute pain after orthopedic surgery compared with placebo. These data suggest that at doses providing comparable efficacy, tapentadol IR 100 mg has improved gastrointestinal tolerability compared with oxycodone HCl IR 15 mg.

PMID: 19203298

Rating: 2b

Dart RC, Bailey E. Does therapeutic use of acetaminophen cause acute liver failure? *Pharmacotherapy*. 2007;27:1219-30.

CONCLUSION: Prospective studies indicated that repeated use of a true therapeutic acetaminophen dosage may slightly increase the level of serum aminotransferase activity, but hepatic failure or death was not reported. Retrospective reports indicated a higher rate of increased serum aminotransferase levels, and several reported associated liver injury and death. The differing results and presence of evidence indicating inaccurate acetaminophen dosage information in some case reports suggests that these cases may be inadvertent overdoses, rather than true therapeutic dosages.

PMID: 17723075

Rating: 1b

DEA. Proposed Rules. Schedules of Controlled Substances: Placement of Tramadol into Schedule IV. Federal Register. 2013 Nov 4; v 78:213:65923-65932.

The Drug Enforcement Administration (DEA) proposes to place the substance 2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol, its salts, isomers, salts of isomers, and all isomeric configurations of possible forms including tramadol (the term "isomers" includes the optical and geometric isomers) into Schedule IV of the Controlled Substances Act (CSA). This proposed action is based on a recommendation from the Assistant Secretary for Health of the Department of Health and Human Services (HHS) and an evaluation of all other relevant data by the DEA. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to Schedule IV controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities, or possess) or propose to handle tramadol.

DeAndrade JR, Maslanka M, Maneatis T, Bynum L, Burchmore M. The use of ketorolac in the management of postoperative pain. *Orthopedics*. 1994 Feb;17(2):157-66.

Ketorolac, when administered intramuscularly, can be used as an alternative to opioid therapy.

PMID: 8190679

Rating: 2b

Deer T, Chapple I, Classen A, et al. Intrathecal Drug Delivery for Treatment of Chronic Low Back Pain: Report From the National Outcomes Registry for Low Back Pain. *Pain Med* 2004;5:6-13.

Background. For 2 decades, implantable drug-delivery systems (IDDSs) have been in use for the management of intractable pain. Results. Thirty-six physicians enrolled 166 patients for trialing (ie, evaluation with a temporary intraspinal analgesic for adequacy of pain relief and acceptable side effects) with IDDS. At 12 months, numeric back-pain ratings for these patients decreased by 48% and leg-pain ratings declined by 32% (Table). The overall pain reduction was 58% at 6 months and 62% at 12 months. Furthermore, at 12 months, 87% of the IDDS patients described their quality of life as fair to excellent, and 87% said they would repeat the implant procedure. Commentary. Although the report is promising and illustrates the importance of longitudinal outcome studies, the follow-up rates fell to 79% at 6 months and 56% at 12 months. The attrition rate not only limits efficacy analyses but also the recognition of complication rates (ie, infection, dislodging, and cerebrospinal fluid leak) that are likely to rise with time in these procedures.

Rating: 3b

Deer T, Krames ES, Hassenbusch SJ, Burton A, Caraway D, Dupen S, Eisenach J, Erdek M, Grigsby E, Kim P, Levy R, McDowell G, Mekhail N, Panchal S, Prager J, Rauck R, Saulino M, Sitzman T, Staats P, Stanton-Hicks M, Stearns L, Willis KD, Witt W, Follett K, Huntoon M, Liem L, Rathmell J, Wallace M, Buchser E, Cousins M, Ver Donck A. Polyanalgesic Consensus Conference 2007: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel. *Neuromodulation: Technology At The Neural Interface*. Volume 10, Number 4, 2007, p. 300-328.

Results: Of note is that the panelists felt that ziconotide, based on new and relevant literature and experience, should be updated to a line one intrathecal drug.

Rating: 8b

PMID: 22150890

Note: *Neurmodualtion* has not yet been accepted for inclusion in MEDLINE, and this "conference" was sponsored by Elan, the manufacturer of Prialt (ziconotide).
Other comments: On pages 313 and 314 it appears the Panel of Experts moved this medication to level 1 based on the following:
1. (Reference 165). This was a case study of one subject (age 13 years) with CRPS.
2. (Reference 169). This study weaned all patients from IT drugs and replaced them with systemic opioids. Clinical judgment was used for this part of the protocol. Inclusion protocol was "severe chronic pain." The double-blind treatment period was 3 weeks. The mean oral morphine equivalents per patient were around 300 mg. At week 1 the difference in pain relief was statistical, but this was not found at week 2. At week 3 the proportion of treatment responders did not differ significantly between the two groups. This was the 3rd double blind, placebo controlled study with Prialt that formed the basis of the recent approval by the FDA.
3. (Reference 166): not listed on PubMed
On page 320 it was noted that Prialt was given a "special box" reference due to limited/targeted use and wide panel of known adverse effects. There is no discussion of dose escalation or opioid hyperalgesia (in reference to morphine). The use of an admixture of morphine and Prialt was based on reference 173, an abstract presentation. The conference was not only supported by Elan but the document clearly was directed at supporting Prialt. The participants are all highly ethical individuals but the document does not represent EBM. The main problem with the Polyanalgesic Conference recommendations is the support by Elan. As an outsider looking at their recommendations, this would appear to potentially undermine some of their suggestions.

Deer T, Kapural L, Sitzman T. AAPM 2009: Specialists Endorse Intrathecal Pain Therapies but Urge Caution. American Academy of Pain Medicine 25th Annual Meeting, Honolulu, Hawaii. Plenary session 112. Presented January 28, 2009.

Presenter Timothy Deer, MD, from the Center for Pain Relief in Charleston, West Virginia, discussed the problem of off-label use of various analgesics with this strategy. "It is important to use an approved catheter with an approved drug," he told the meeting. "Clinicians are putting drugs in the pumps with absolutely no reasoning for it and are doing some outrageous things." There are currently only 2 drugs approved by the US Food and Drug Administration for use in intrathecal pumps — morphine and ziconotide. Dr. Kapural suggested that intrathecal therapies should be considered a last step in the treatment of cancer and noncancer pain. "When you've been practicing long enough, it's not a question of if but when you are going to see complications" associated with intrathecal treatment, Todd Sitzman, MD, from the Forrest General Cancer Center, in Hattiesburg, Mississippi, said during his talk. To reduce postoperative mortality associated with intrathecal pain treatment, Dr. Sitzman urged clinicians to "start low and go slow."

Rating: 10b

Dell'Osso B, Altamura AC, Mundo E, Marazziti D, Hollander E. Diagnosis and treatment of obsessive-compulsive disorder and related disorders. *Int J Clin Pract*. 2007;61:98-104.

Obsessive-compulsive related disorders (OCRDs), often comorbid with OCD, include many distinct psychiatric conditions (i.e. some somatoform disorders, eating disorders, impulse control disorders and some neurological conditions) which have overlapping symptoms and compulsive qualities with OCD.

PMID: 17229184

Rating: 5c

de Mos M, Sturkenboom MC, Huygen FJ. Current understandings on complex regional pain syndrome. *Pain Pract*. 2009;9:86-99.

PMID: 19215592

The authors state that extreme fear for pain can lead to disuse of the affected limb. They postulate that this could make a feasible contribution to the outcome of CRPS. They also discuss prolonged immobilization.

Rating: 5b

Denis C, Fatséas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings*. Cochrane Database Syst Rev*. 2006;3:CD005194.

CONCLUSIONS: The results of this systematic review point to the potential value of carbamazepine as an effective intervention for benzodiazepine gradual taper discontinuation.

PMID: 16856084

Rating: 1a

Dersh J, Gatchel RJ, Mayer T, Polatin P, Temple OR. Prevalence of psychiatric disorders in patients with chronic disabling occupational spinal disorders. *Spine*. 2006 May 1;31(10):1156-62.

CONCLUSIONS: Failure to follow a biopsychosocial approach to treatment will likely contribute to prolonged disability in a substantial number of these chronic pain patients.

PMID: 16648753

Rating: 4a

Dersh J, Gatchel RJ, Polatin P, Mayer T. Prevalence of psychiatric disorders in patients with chronic work-related musculoskeletal pain disability. *J Occup Environ Med*. 2002 May;44(5):459-68.

A majority (64%) of patients were diagnosed with at least one current disorder, compared with only 15% of the general population. However, prevalences of psychiatric disorders were elevated in patients only after the work-related disability.

PMID: 12024691

Rating: 4a

Dersh J, Mayer T, Gatchel RJ, Towns B, Theodore B, Polatin P. Psychiatric comorbidity in chronic disabling occupational spinal disorders has minimal impact on functional restoration socioeconomic outcomes. *Spine.* 2007;32:1917-25.

CONCLUSIONS: Poorer work outcomes were more common with specific (and comorbid) Axis I psychiatric disorders. Opioid dependence was the single disorder associated most often with less successful outcomes.

PMID: 17762302

Rating: 4a

Dersh J, Mayer TG, Gatchel RJ, Polatin PB, Theodore BR, Mayer EA. Prescription opioid dependence is associated with poorer outcomes in disabling spinal disorders. *Spine.* 2008;33:2219-27.

CONCLUSIONS: Iatrogenic prescription opioid dependence may be a risk factor for less successful long-term work and health outcomes, even after detoxification from opioids as part of an interdisciplinary functional rehabilitation program. Chronic prescription opioid dependence in this patient population is also associated with a significantly higher prevalence of comorbid psychiatric conditions, both axis I and II.

PMID: 18725868

Rating: 3a

Devleeschouwer V, Roelandts R, Garmyn M, Goossens A. Allergic and photoallergic contact dermatitis from ketoprofen: results of (photo) patch testing and follow-up of 42 patients. *Contact Dermatitis*. 2008;58:159-66.

Photoallergic contact dermatitis from topical ketoprofen (KP), a nonsteroidal anti-inflammatory agent, is a well-known side effect. The severe clinical symptoms sometimes require hospitalization, and/or systemic corticosteroids.

PMID: 18279154

Rating: 4a

Diaz RL, Gardeazabal J, Manrique P, Ratón JA, Urrutia I, Rodríguez-Sasiain JM, Aguirre C. Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis.* 2006;54:239-43.

The use of topical non-steroidal anti-inflammatory drugs (NSAIDs) is very popular in spite of their doubtful efficacy and high number of generally not serious, but preventable, adverse effects, especially photoallergy. A total of 139 contact reactions to topical NSAIDs were found with ketoprofen being responsible for 28% of the allergies and 82% of the contact photoallergies in spite of not being the most used topical NSAID (third in the ranking, diclofenac was the first). The results support the need for regulatory action on topical ketoprofen.

PMID: 16689806

Rating: 4b

Dickenson WE, Eickelberg SJ. Management of sedative-hypnotic intoxication and withdrawal. In Reis RK, Fiellin DA, Miller SC, Saitz R. eds. *Principles of Addiction Medicine*, 4th edition. Lippincott Williams & Wilkins, 2009.

Rating: 9a

Distel LM, Best TM. Prolotherapy: a clinical review of its role in treating chronic musculoskeletal pain. *PM R*. 2011 Jun;3(6 Suppl 1):S78-81.

Additional larger, randomized controlled trials are needed to make specific recommendations regarding ideal protocols and indications.

PMID: 21703585

Rating: 5b

Doe-Simkins M, Quinn E, Xuan Z, Sorensen-Alawad A, Hackman H, Ozonoff A, Walley AY. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: a retrospective cohort study. BMC Public Health. 2014;14:297.

PMID: 24684801

Rating: 3a

Doleys DM, Dinoff BL. Psychological aspects of interventional therapy. *Anesthesiol Clin North America*. 2003 Dec;21(4):767-83.

Even when used for diagnostic or prognostic purposes, the impact of psychosocial variables and the potential relevance of a meaningful behavioral or psychologic evaluation cannot be overstated.

PMID: 14719718

Rating: 5a

Donnellan C, Preston C, Moayyedi P, Sharma N. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *Cochrane Database Syst Rev.* 2010 Feb 17;2:CD003245.

CONCLUSIONS: Healing doses of PPIs are more effective than all other therapies, although there is an increase in overall adverse effects compared to placebo.

PMID: 20166065

Rating: 1b

Dros J, Wewerinke A, Bindels PJ, van Weert HC. Accuracy of monofilament testing to diagnose peripheral neuropathy: a systematic review. *Ann Fam Med.* 2009 Nov-Dec;7(6):555-8.

RESULTS: We reviewed 173 titles and abstracts of articles to identify 54 potentially eligible studies. CONCLUSIONS: Accordingly, we do not recommend the sole use of monofilament testing to diagnose peripheral neuropathy.

PMID: 19901316

Rating: 1b

Drucker AM, Rosen CF. Drug-induced photosensitivity: culprit drugs, management and prevention. *Drug Saf*. 2011;34:821-37

PMID: 21879777

Rating: 5b

Dubinsky RM, Miyasaki J. Assessment: efficacy of transcutaneous electric nerve stimulation in the treatment of pain in neurologic disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2010 Jan 12;74(2):173-6. Epub 2009 Dec 30.

RECOMMENDATIONS: Transcutaneous electric nerve stimulation (TENS) is not recommended for the treatment of chronic low back pain (Level A). TENS should be considered in the treatment of painful diabetic neuropathy (Level B).

PMID: 20042705

Rating: 1b

Ducharme S, Fraser R, Gill K. Update on the clinical use of buprenorphine: in opioid-related disorders. *Can Fam Physician*. 2012 Jan;58(1):37-41.

PMID: 22267618

Rating: 5b

Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol.* 2003 Nov;60(11):1524-34.

Randomized controlled clinical trials of gabapentin, the 5% lidocaine patch, opioid analgesics, tramadol hydrochloride, and tricyclic antidepressants provide an evidence-based approach to the treatment of neuropathic pain, and specific recommendations are presented for use of these medications.

PMID: 14623723

Rating: 5a

Dworkin RH, O'connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain*. 2007 Dec 5;132(3):237-51.

Recommended first-line treatments include certain antidepressants (i.e., tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel alpha2-delta ligands (i.e., gabapentin and pregabalin), and topical lidocaine. To date, no medications have demonstrated efficacy in lumbosacral radiculopathy, which is probably the most common type of NP. Long-term studies, head-to-head comparisons between medications, studies involving combinations of medications, and RCTs examining treatment of central NP are lacking and should be a priority for future research.

PMID: 17920770

Rating: 1b

Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc*. 2010;85:S3-14. Review.

Opioid analgesics and tramadol were recommended as second-line treatments that can be considered for first-line use in certain clinical circumstances.

PMID: 20194146

Rating: 5b

Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, Levy RM, Backonja M, Baron R, Harke H, Loeser JD, Treede RD, Turk DC, Wells CD. Interventional management of neuropathic pain: NeuPSIG recommendations. *Pain*. 2013 Jun 5. doi:pii: S0304-3959(13)00297-2.

PMID: 23748119

Rating: 1c

Dyck PJ, Norell JE, Dyck PJ. Non-diabetic lumbosacral radiculoplexus neuropathy: natural history, outcome and comparison with the diabetic variety. *Brain.* 2001 Jun;124(Pt 6):1197-207.

PMID: 11353735

Rating: 4b

Dysvik E, Natvig GK, Eikeland OJ, Brattberg G. Results of a multidisciplinary pain management program: a 6- and 12-month follow-up study. *Rehabil Nurs*. 2005 Sep-Oct;30(5):198-206.

PMID: 16175925

Rating: 4b

Edwards JE, Oldman A, Smith L, Collins SL, Carroll D, Wiffen PJ, McQuay HJ, Moore RA. Single dose oral aspirin for acute pain. *The Cochrane Database of Systematic Reviews* 2006 Issue 3

Aspirin is an effective analgesic for acute pain of moderate to severe intensity with a clear dose-response. Drowsiness and gastric irritation were seen as significant adverse effects even though the studies were single-dose. The pain relief achieved with aspirin was very similar milligram for milligram to that seen with paracetamol.

Rating 1a

Eisenberg E, **River Y**, **Shifrin A**, **Krivoy N**. **Antiepileptic drugs in the treatment of neuropathic pain. *Drugs*. 2007:67(9):1265-89.**

Trials with long-term follow-up are required to establish the long-term efficacy of antiepileptic drugs in neuropathic pain.

PMID: 17547471

Rating: 5a

Ellenbecker CH, Samia L, Cushman MJ, et al. Patient Safety and Quality in Home Health Care. In: Hughes RG, editor. Patient Safety and Quality: An Evidence-Based Handbook for Nurses. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Apr. Chapter 13.

PMID: 21328733

Rating: 8a

Erdogan M, Erdogan A, Erbil N, Karakaya HK, Demircan A. Prospective, Randomized, Placebo-controlled Study of the Effect of TENS on postthoracotomy pain and pulmonary function. *World J Surg*. 2005 Dec;29(12):1563-70.

Additionally, following the sixth postoperative hour, TENS increased the spirometric breath function.

PMID: 16331341

Rating: 2c

Erman MK. Therapeutic options in the treatment of insomnia. J Clin Psychiatry. 2005;66 Suppl 9:18-23.

Although antidepressants, antipsychotics, and anticonvulsants are often prescribed for the treatment of insomnia, they are not approved by the U.S. Food and Drug Administration for this indication and have side effects that are sometimes severe.

Rating 5b

Esenyel M, Caglar N, Aldemir T. Treatment of myofascial pain. *Am J Phys Med Rehabil*. 2000;79:48-52.

CONCLUSIONS: Patients with myofascial pain syndrome had higher scores for anxiety than for depression.

PMID: 10678603

Rating: 2b

Esparza F, Cobián C, Jiménez JF, García-Cota JJ, Sánchez C, Maestro A; Working group for the acute pain study of SETRADE. Topical ketoprofen TDS patch versus diclofenac gel: efficacy and tolerability in benign sport related soft-tissue injuries. *Br J Sports Med*. 2007;41:134-9.

The ketoprofen patch was not inferior to diclofenac gel in reducing the baseline pain during daily activities. Ketoprofen patch presented also a higher cure rate (64%) than diclofenac gel (46%) at day 7. Patient opinions about the treatment comfort were also statistically higher for the ketoprofen patch.

PMID: 17138642

Rating: 2c

Ettinger AB, Argoff CE. Use of antiepileptic drugs for nonepileptic conditions: psychiatric disorders and chronic pain. *Neurotherapeutics*. 2007 Jan;4(1):75-83.

Underlying depression and anxiety symptoms may be exacerbated by levetiracetam, while psychotic symptoms have rarely been reported with topiramate, levetiracetam, and zonisamide

PMID: 17199018

Rating: 5b

FDA. The Acetaminophen Hepatotoxicity Working Group Center for Drug Evaluation and Research. Recommendations for FDA Interventions to Decrease the Occurrence of Acetaminophen Hepatotoxicity. February 26, 2008.
This report represents the recommendations of a working group asked by former CDER Director Dr.
Steven Galson to consider FDA interventions that could decrease the number of cases of unintentional
and intentional overdose leading to liver injury from over-the-counter and prescription drug products. CDER recognizes that acetaminophen-related hepatotoxicity is a significant public health problem.

Rating: 10a

FDA. Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS). January - March 2008

The table below lists the names of products and potential signals of serious risks/new safety information that were identified for these products during the period January - March 2008 in the AERS database.

Potential Signals of Serious Risks/New Safety Information Identified by the Adverse Event Reporting System (AERS) January - March 2008

Product Name: Active Ingredient (Trade) *or* Product Class	**Potential Signal of Serious Risk/New Safety Information**
Duloxetine (Cymbalta)	Urinary retention
Oxycodone Hydrochloride Controlled-Release (Oxycontin)	Drug misuse, abuse and overdose
Tumor Necrosis Factor (TNF) Blockers	Cancers in children and young adults

Rating: 8a

FDA News. FDA Approves First Drug for Treating Fibromyalgia. June 21, 2007

Two double-blind, controlled clinical trials, involving about 1,800 patients, support approval for use in treating fibromyalgia with doses of 300 milligrams or 450 milligrams per day.

Rating: 8b

FDA News. FDA approves Botox to treat chronic migraine, Oct. 15, 2010

Botox is given approximately every 12 weeks as multiple injections around the head and neck to try to dull future headache synmptoms. Botox ha not been shown to work for the treatment of migraine headaches that occur 14 days or less per month, or for other forms of headache.

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229782.htm

Rating:

Federation of State Medical Boards, ***Model Guidelines for the Use of Controlled Substances for the Treatment of Pain,*** March 23, 2004

"State medical boards recognize undertreatment of pain as a public health priority," said James N. Thompson, M.D., chief executive officer for the Federation of State Medical Boards. "They actively support pain management as an important part of good medical practice." Today, underprescribing those same medications is considered as much a breach of the appropriate standard of care as overprescribing. In fact, the Oregon and California medical boards already have disciplined physicians for the undertreatment of pain and New Mexico revised its medical practice act to specify that undertreatment of pain may be grounds for unprofessional conduct.

Rating: 5b

Feinberg SD. ACPA Chronic Pain Medications Supplement. American Chronic Pain Association, Inc. 2008

The ACPA Chronic Pain Medications Supplement 2008 provides a short review of all available medication treatments for pain in patient-oriented language.

Rating: 8b

Ferrante FM, Bearn L, Rothrock R, King L. Evidence against trigger point injection technique for the treatment of cervicothoracic myofascial pain with botulinum toxin type A. *Anesthesiology.* 2005 Aug;103(2):377-83.

UCLA Pain and Spine Care, Department of Anesthesiology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA. mferrante@mednet.ucla.edu

METHODS: The study goal was to determine whether direct injection of botulinum toxin type A (BoNT-A) into trigger points was efficacious for cervicothoracic myofascial pain, and if so, to determine the presence or absence of a dose-response relation. CONCLUSIONS: Injection of BoNT-A directly into trigger points did not improve cervicothoracic myofascial pain. The role of direct injection of trigger points with BoNT-A is discussed in comparison to other injection methodologies in the potential genesis of pain relief.

PMID: 16052120

Rating: 2c

Feuerstein M, Berkowitz SM, Haufler AJ, Lopez MS, Huang GD.Working with low back pain: workplace and individual psychosocial determinants of limited duty and lost time. *American Journal of Independent Medicine*. 2001 Dec;40(6):627-38.

CONCLUSIONS: The results support the potential utility of interventions targeting ergonomic, workplace and individual psychosocial risk factors in secondary prevention.

PMID: 11757039

Publication Type: Case Control, 421 cases

Fingerhut L. Increases in poisoning and methadone-related deaths: United States, 1999-2005. Hyattsville, MD: Centers for Disease Control and Prevention's National Center for Health Statistics. 2008.

Rating: 8b

Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain.* 2005 Dec 5;118(3):289-305. Epub 2005 Oct 6.

One hundred and five studies were included. In peripheral neuropathic pain, the lowest NNT was for tricyclic antidepressants, followed by opioids and the anticonvulsants gabapentin and pregabalin.

PMID: 16213659

Rating: 5a

Finnerup NB, Otto M, Jensen TS, Sindrup SH. An evidence-based algorithm for the treatment of neuropathic pain. *MedGenMed.* 2007 May 15;9(2):36.

METHOD: A treatment algorithm for neuropathic pain was formulated on the basis of a review of 105 high-quality, randomized, placebo-controlled clinical trials. RESULTS: TCAs had the lowest NNT followed by opioids and AEDs, such as gabapentin and pregabalin.

PMID: 17955091

Rating: 1b

Finsen V, Persen L, Lovlien M, Veslegaard EK, Simensen M, Gasvann AK, Benum P. Transcutaneous electrical nerve stimulation after major amputation. *J Bone Joint Surg Br*. 1988 Jan;70(1):109-12.

Sham TENS had a considerable placebo effect on pain. There were, however, no significant differences in the analgesic requirements or reported prevalence of phantom pain between the groups during the first four weeks.

PMID: 3257494

Rating: 2c

Fishbain D, Evidence-based data on pain relief with antidepressants, *Ann Med.* 2000 Jul;32(5):305-16.

Finally, this evidence indicated that antidepressants could be effective for pain associated with some specific pain syndromes, such as chronic low back pain, osteoarthritis or rheumatoid arthritis, fibrositis or fibromyalgia, and ulcer healing.

PMID: 10949061

Rating: 5b

Fishbain DA, Lewis JE, Cole B, Cutler B, Rosomoff HL, Rosomoff RS. Lidocaine 5% patch: an open-label naturalistic chronic pain treatment trial and prediction of response. *Pain Med*. 2006;7:135-42.

CONCLUSIONS: A significant percentage of CPPs exposed to an L5P 3-day naturalistic trial perceived clinical improvement. However, this can only be concluded as an initial effect, and whether or not this effect is attributable to L5P cannot be derived from our data as the effect could have been nonspecific.

PMID: 16634726

Rating: 4c

Fisher R, Hassenbusch S, Krames E, Leong M, Minehart M, Prager J, Staats P, Webster L, Willis KD.A Consensus Statement Regarding the Present Suggested Titration for Prialt (Ziconotide). *Neuromodulation* 2005; 8:153–154.

This was a titration that stated the following: *Because of the side-effect profile of this drug, the recommended **maximum** titration rate approved by the FDA on December 28, 2004 and stated in the package insert is considered, unanimously, by the undersigned authors of this editorial and the vast majority of Prialt clinical investigators, to be two and one-half to five times too rapid.* They also stated: *Given the severity of the side-effects of this drug, it is recommended by a consensus of the most experienced clinical investigators (signatures below), that the "mantra" regarding the initiation of intrathecal Prialt for pain control should be to "Start Low and Go Slo.* The rinse process is also very important to the infusion of this drug.

Rating: 8a

Flor H, Fydrich T, Turk DC. Efficacy of multidisciplinary pain treatment centers: a meta-analytic review. *Pain.* 1992 May;49(2):221-30.

The beneficial effects of multidisciplinary treatment were not limited to improvements in pain, mood and interference but also extended to behavioral variables such as return to work or use of the health care system.

PMID: 1535122

Rating: 1a

Flor H, Birbaumer N. Comparison of the efficacy of electromyographic biofeedback, cognitive-behavioral therapy, and conservative medical interventions in the treatment of chronic musculoskeletal pain. *J Consult Clin Psychol*. 1993 Aug;61(4):653-8.

Results suggest that pain patients who suffer from musculoskeletal pain problems and display few physical disabilities may profit the most from short-term EMG biofeedback treatment.

PMID: 8370861

Rating: 2c

Fock KM, Katelaris P, Sugano K, Ang TL, Hunt R, Talley NJ, Lam SK, Xiao SD, Tan HJ, Wu CY, Jung HC, Hoang BH, Kachintorn U, Goh KL, Chiba T, Rani AA; Second Asia-Pacific Conference.Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. *J Gastroenterol Hepatol*. 2009;24:1587-600.

It was recommended that H. pylori infection should be tested for and eradicated prior to long-term aspirin or non-steroidal anti-inflammatory drug therapy in patients at high risk for ulcers and ulcer-related complications.

PMID: 19788600

Rating: 8b

Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med.* 2007;167:394-9.

CONCLUSIONS: The frequency of nonnarcotic analgesic use is independently associated with a moderate increase in the risk of incident hypertension.

PMID: 17325302

Rating: 3a

Forouzanfar T, Kemler MA, Weber WE, Kessels AG, Van Kleef M, Spinal cord stimulation in complex regional pain syndrome: cervical and lumbar devices are comparably effective, *Br J Anaesth*. 2004 Jan 22

RESULTS: According to the GPE, at least 42% of the cervical SCS patients and 47% of the lumbar SCS patients reported at least 'much improvement'. Complications and adverse effects occurred in 64% of the patients and consisted mainly of technical defects.

PMID: 14742334

Rating: 4c

Forouzanfar T, Köke AJ, van Kleef M, Weber WE. Treatment of complex regional pain syndrome type I. *Eur J Pain*. 2002;6:105-22.

Controversy exists about the effectiveness of therapeutic interventions for the management of RSD/CRPS I.

PMID: 11900471

Rating: 1b

Feuerstein TJ, Chronic pain treatment with antidepressants – Metaanalysis. *Schmerz.* 1997 Jun 13;11(3):213-26.

Both preclinical and clinical evidence support the usefulness of antidepressants in chronic pain treatment. 57 Clinical trials were separated into 5 groups according to their scientific quality. The most effective antidepressants in chronic pain treatment only included unselective monoamine reuptake inhibitors in the following rank order: amitriptyline > clomipramine >/= desipramine >/= imipramine >/= doxepin.

PMID: 12799822

Rating: 1b

Frank D, Mateu-Gelabert P, Guarino H, Bennett A, Wendel T, Jessell L, Teper A. High risk and little knowledge: overdose experiences and knowledge among young adult nonmedical prescription opioid users. Int J Drug Policy. 2015;26:84-91.

PMID: 25151334

Rating: 11a

Fredheim OM, Moksnes K, Borchgrevink PC, Kaasa S, Dale O. Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand.* 2008 Mar 6; [Epub ahead of print].

Conclusion: In spite of challenges related to the variable pharmacokinetics and concerns regarding increase in QTc time, current evidence indicates that opioid switching to methadone improves pain control in a substantial proportion of patients who are candidates for opioid switching.

PMID: 18331375

Rating: 1c

Freeman R, Durso-Decruz E, Emir B. Efficacy, safety and tolerability of pregabalin treatment of painful diabetic peripheral neuropathy: findings from 7 randomized, controlled trials across a range of doses. Diabetes Care. 2008 Mar 20 [Epub ahead of print].

CONCLUSIONS Treatment with pregabalin across its effective dosing range is associated with significant, dose-related improvement in pain in patients with DPN.

PMID: 18356405

Rating: 1b

Friedman AP, DiSerio FJ. Symptomatic treatment of chronically recurring tension headache: a placebo-controlled, multicenter investigation of Fioricet and acetaminophen with codeine. *Clin Ther.* 1987;10(1):69-81.

Fioricet, but not acetaminophen with codeine, was significantly better than placebo in alleviating emotional or psychic tension; Fioricet was also significantly better than acetaminophen with codeine in relieving this symptom.

PMID: 3329967

Rating: 2b

Friedman MJ. **PTSD: Pharmacotherapeutic Approaches. *Focus.* 2013;11(3):315-320.**

Rating: 8a

Fritz JM, Cleland JA, Brennan GP. Does adherence to the guideline recommendation for active treatments improve the quality of care for patients with acute low back pain delivered by physical therapists? *Med Care.* 2007 Oct;45(10):973-80.

CONCLUSIONS: Adherence to the guideline recommendation for active care was associated with better clinical outcomes and reduced cost.

PMID: 17890995

Rating: 4a

Frost H, Lamb SE, Klaber Moffett JA, Fairbank JC, Moser JS. A fitness programme for patients with chronic low back pain: 2-year follow-up of a randomised controlled trial. *Pain.* 1998;75:273-9.

Between group comparisons demonstrated a statistically significant difference in disability scores between the treatment and control group (mean difference 5.8, 95% confidence interval 0.3, 11.4 P < 0.04).

PMID: 9583763

Rating: 2c

Furlan AD, Sandoval JAS, Mailis A. Spinal cord stimulation for chronic pain (Protocol for a Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Spinal Cord Stimulation (SCS), first called Dorsal Column Stimulation (DCS), 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 wide spectrum of pain diagnoses, probably indiscriminately. The results at follow-up were poor and the method soon fell in disrepute. As a result, in the late 1970s and 1980s SCS was, at least in the United States, still used in only few specialized pain centers. In Europe, SCS was not introduced until the early 1970s and then practiced to a very limited extent. 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 reoperations 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. SCS involves the use of an electrical generator which delivers pulses by means of an electrode placed in the epidural space adjacent to a targeted spinal cord area, which is causing the pain. The leads, which are special devices containing the set of electrodes, can be implanted by laminectomy or percutaneously. Nowadays, protocols for SCS implantation stipulate a screening trial period with temporary percutaneous placement of the leads and using an external generator. Despite the limited evidence for SCS efficacy because of the lack of controlled studies, the use of spinal stimulation for pain relief has increased exponentially during the last decade. In 1995 it was estimated that 14000 stimulators were being implanted worldwide each year and in Europe in 1997 the figure was 5000 units per annum. Since the publication of Turner's review a number of clinical trials have been published, and it is the objective of this review to assess the current evidence.

Rating: 5b

Furlan AD, Mailis A, Papagapiou M. Are we paying a high price for surgical sympathectomy? A systematic literature review of late complications. *J Pain*. 2000 Winter;1(4):245-57.

The main indication was primary hyperhidrosis in 84.3% of the patients. Surgical sympathectomy, irrespective of approach, is accompanied by several potentially disabling complications. Detailed informed consent is recommended when surgical sympathectomy is contemplated.

PMID: 14622605

Rating: 1c

Furlan AD, Sjölund BH. Igniting the spark? Pain. 2007 Jul;130(1-2):1-3. Epub 2007 May 22.

Comment on: Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: A meta-analysis of randomized controlled trials. Pain. 2007 Jul;130(1-2):157-65.

PMID: 17521812

Rating: 11b

There has been another letter to the editor about this article from Furlan et al. They state the following:
1. The methodological quality of the studies that the meta-analysis was based on was low.
2. There was still a need to demonstrate the benefits of ENS to other modalities to assess the pain conditons that are most responsive
3. What is the most appropriate duration.
This author did not pick up the above discrepencies in disease states.
Furlan writes for Cochrane

Editorial -- Igniting the spark?
In the past, the evidence about the effectiveness of electrical nerve stimulation (ENS) for the treatment of pain was combined in various systematic reviews of randomized controlled trials (RCTs). However most of these systematic reviews focused on a specific regional pain condition or a particular type of ENS and therefore were not able to combine the studies using statistical methods because they included only a subset of RCTs. On the other hand, some people view this as a disadvantage, because combining different studies may neutralize a negative study with a positive study, meaning that clinically important differences might explain differences and therefore it is not appropriate to combine heterogeneous studies. There is still a need to demonstrate the benefits of ENS compared to other modalities and therapies, to assess what kind of pain conditions are most responsive to ENS and to estimate the most appropriate duration of therapy.

Furukawa TA, Watanabe N, Churchill R. Combined psychotherapy plus antidepressants for panic disorder with or without agoraphobia. *Cochrane Database Syst Rev*. 2007;(1):CD004364.

RESULTS: After termination of the acute phase and continuation treatment, the combined therapy was more effective than pharmacotherapy alone and was as effective as psychotherapy.

PMID: 17253502

Rating: 1b

Gaines, J., et al. The Effect of Neuromuscular Electrical Stimulation on Arthritis Knee Pain in Older Adults with Osteoarthritis of the Knee. *Applied Nursing Research* 2004. August; Volume 17, Number 3: 201-06.

Rating: 2c

Quality: Low. Total Rating: 3.0. Comment: Does not meet inclusion criteria for evidence-based review.

Galantino ML, Bzdewka TM, Eissler-Russo JL, Holbrook ML, Mogck EP, Geigle P, Farrar JT, The impact of modified Hatha yoga on chronic low back pain: a pilot study, *Altern Ther Health Med.* 2004 Mar-Apr;10(2):56-9.

CONCLUSION: A modified yoga-based intervention may benefit individuals with CLB, but a larger study is necessary to provide definitive evidence.

PMID: 15055095

Rating: 2c

Galer BS, Bruehl S, Harden RN. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. International Association for the Study of Pain. *Clin J Pain.* 1998 Mar;14(1):48-54.

Data analysis suggested that CRPS decision rules may lead to overdiagnosis of the disorder. Diagnosis based on self-reported symptoms can be diagnostically useful in some circumstances.

PMID: 9535313

Rating: 4b

Galer BS, Gammaitoni AR, Oleka N, Jensen MP, Argoff CE. Use of the lidocaine patch 5% in reducing intensity of various pain qualities reported by patients with low-back pain. *Curr Med Res Opin*. 2004;20 Suppl 2:S5-12.

CONCLUSIONS: In patients with moderate-to-severe LBP, 2 weeks and 6 weeks of treatment with the lidocaine patch 5% significantly reduces the intensity of pain qualities as measured by all 4 NPS composite measures.

PMID: 1556374

Rating: 4c

The Neuropathic Pain Scale was utilized to assess inclusion in this study and used as an outcome. The study was funded and written by Endo Pharmaceuticals.

Gallagher RM. Primary care and pain medicine. A community solution to the public health problem of chronic pain. *Medical Clinics of North America*. 01-May-1999; 83(3): 555-83, v.

The author emphasizes that pain is an important public health problem that demands attention. He discusses ineffective management and its causes, administrative and socioeconomic problems perpetuating poor care, problems in technology transfer, organizational models, specialists and subspecialists, and other topics.

Publication Type: Review

Gallagher RM. Treatment planning in pain medicine. Integrating medical, physical, and behavioral therapies. *Medical Clinics of North America.* 01-May-1999; 83(3): 823-49, viii.

Creating attitudes of self-help through knowledge and pain management training is complementary to the selective use of the advances in technology that have occurred in response to the explosion of neurosciences and clinical research.

Rating: 5b

Gallagher RM, Rauh V, Haugh LD, Milhous R, Callas PW, Langelier R, McClallen JM, Frymoyer J. Determinants of return-to-work among low back pain patients. *Pain*. 1989;39(1):55-67.

The data suggest that exclusive reliance on the physical examination to determine level of disability, without consideration of psychosocial conditions, and without adjusting for the confounding effects of age and length of time out-of-work, is not empirically justified.

PMID: 2530487

Rating: 3b

Gammaitoni A, Gallagher RM, Welz-Bosna M. Topical ketamine gel: possible role in treating neuropathic pain. *Pain Med*. 2000;1:97-100.

Until further information is available and larger trials can be conducted, we can only recommend this type of therapy for refractory cases in which all primary and secondary options have been exhausted.

PMID: 15101968

Rating: 5c

García Rodríguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet*. 1994;343:769-72. Erratum in: *Lancet* 1994 Apr 23;343(8904):1048.

NSAIDS should be used cautiously in patients who have other risk factors for UGIB; these include advanced age, smoking, history of peptic ulcer, and use of oral corticosteroids or anticoagulants.

PMID: 7907735

Rating: 3a

Gatchel RJ; Gardea MA. Psychosocial issues: their importance in predicting disability, response to treatment, and search for compensation. *Neurologic Clinics.* 01-Feb-1999; 17(1): 149-66

The conceptualization of pain and its progression into chronic disability has evolved from unidimensional models to more integrative, biopsychosocial models that take into account the many biological, psychosocial, social, and economic factors that may significantly contribute to the low back pain experience. Further, we examine the issue of compensation and how it too is intricately intertwined with the other variables contributing to lower back pain disability.

Publication Type: Review

Gatchel R., Polatin P. and Kinney R. Predicting Outcome of Chronic Back Pain Using Clinical Predictors of Psychopathology: A Prospective Analysis. *Health Psychology* 1995:14 (5);415-20.

These results demonstrate the presence of a psychosocial disability variable that is associated with those injured workers who are likely to develop chronic disability problems.

Rating: 3b, 324 cases

Authors' conclusions: Psychosocial variables more important in development of back pain-related disability than injury severity and job demands. Comments: Cannot infer what psychosocial information ought to be elicited at initial office visit; SCID and MMPI not practical for routine clinical use

Gatchel RJ, Mayer TG, Kidner CL, McGeary DD. Are gender, marital status or parenthood risk factors for outcome of treatment for chronic disabling spinal disorders? *J Occup Rehabil.* 2005 Jun; 15(2):191-201.

Thus, in spite of the societal belief to the contrary, it seems that single parent patients can show similar chronic pain rehabilitation outcomes, relative to other CDWRSD patients, after a prescribed course of tertiary functional restoration rehabilitation.

PMID: 15844676

Rating: 4b

Gatchel RJ. Psychosocial factors that can influence the self-assessment of function. *J Occup Rehabil.* 2004 Sep;14(3):197-206.

The present article reviews the major psychosocial barriers to assessment/recovery that have been implicated as influencing the self-assessment of function.

PMID: 15156778

Rating: 5a

Gatchel RJ, Polatin PB, Noe C, Gardea M, Pulliam C, Thompson J. Treatment- and cost-effectiveness of early intervention for acute low-back pain patients: a one-year prospective study. *J Occup Rehabil*. 2003 Mar;13(1):1-9.

Results clearly indicated that the high-risk subjects who received early intervention displayed statistically significant fewer indices of chronic pain disability on a wide range of work, healthcare utilization, medication use, and self-report pain variables, relative to the high-risk subjects who do not receive such early intervention. In addition, the high-risk nonintervention group displayed significantly more symptoms of chronic pain disability on these variables relative to the initially low-risk subjects. Cost-comparison savings data were also evaluated.

PMID: 12611026

Rating: 3c

Gatchel RJ. 2005. *Clinical Essentials of Pain Management*. Washington, DC: American Psychological Association; 2005.

Going beyond traditional biomedical remedies, Robert Gatchel offers a comprehensive viewpoint that takes into consideration not only biological, but also psychological and social variables.

Rating: 9b

Gatchel RJ, Mayer TG, Theodore BR. The pain disability questionnaire: relationship to one-year functional and psychosocial rehabilitation outcomes. *J Occup Rehabil*. 2006 Mar;16(1):75-94.

RESULTS: Lower rates of work retention were associated with more severe pre-treatment PDQ scores. Higher post-treatment PDQ were associated with decreased return-to-work rates, decreased work retention and a greater percentage seeking health care from a new provider. In addition, PDQ scores were also associated with psychosocial measures such as depression and perceived pain intensity, as well as alternative measures of disability.

PMID: 16752090

Rating: 3c

Gavin, I., et al. Identification of Human Cell Responses to Hexavalent Chromium. *Environmental and Molecular Mutagenesis*. 2007. Volume 48: 650-57.

Rating: 5c

Quality: N/A. Total Rating: N/A. Comment: Does not meet inclusion criteria for evidence-based review.

Ghoname EA, Craig WF, White PF, Ahmed HE, Hamza MA, Henderson BN, Gajraj NM, Huber PJ, Gatchel RJ, Percutaneous electrical nerve stimulation for low back pain: a randomized crossover study, *JAMA* 1999 Mar 3;281(9):818-23

The study concluded, “In this sham-controlled study, PENS was more effective than TENS or exercise therapy in providing short-term pain relief and improved physical function in patients with long-term LBP.”

PMID: 10071003

Rating: 2c, RCT, 60 cases

Comments: “Radiologically confirmed” disk disease may not be valid classification, since imaging tests not shown to identify discogenic pain. TENS usually applied prn; this trial applied TENS on fixed schedule & does not constitute a valid comparison of PENS with actual TENS use

Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, Gracely RH, Clauw DJ. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. *Arthritis Rheum*. 2003 Oct;48(10):2916-22.

CONCLUSION: These data help support the clinical impression that there are distinct subgroups of patients with fibromyalgia. There appears to be a group of fibromyalgia patients who exhibit extreme tenderness but lack any associated psychological/cognitive factors, an intermediate group who display moderate tenderness and have normal mood, and a group in whom mood and cognitive factors may be significantly influencing the symptom report.

PMID: 14558098

Rating: 3b

Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry*. 2004 Sep;161(9):1537-47.

CONCLUSIONS: Antidepressants are effective in the short-term treatment of bipolar depression. The trial data do not suggest that switching is a common early complication of treatment with antidepressants. It may be prudent to use a selective serotonin reuptake inhibitor or a monoamine oxidase inhibitor rather than a tricyclic antidepressant as first-line treatment.

PMID: 15337640

Rating: 1b

Gillis, B., et al. Identification of Human cell responses to benzene and benzene metabolites. *Genomics*. 2007. Number 90: 324-33.

Rating: 5c

Quality: N/A. Total Rating: N/A. Comment: Does not meet inclusion criteria for evidence-based review.

Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med.* 2005 Mar 31;352(13):1324-34.

CONCLUSIONS: Gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent, with constipation, sedation, and dry mouth as the most frequent adverse effects.

PMID: 15800228

Rating: 2b

Clinical Question: Is the combination of gabapentin (Neurontin) and morphine more effective for neuropathic pain than either drug alone? Synopsis: Gabapentin and morphine are widely used for neuropathic pain, but it is unclear whether the combination is better than either drug alone. Bottom Line: The combination of gabapentin and morphine provides a small but clinically unimportant benefit over either drug alone. Tricyclic antidepressants have been shown in other studies to be as effective as gabapentin and are much less expensive, but were not studied in this trial. (Level of Evidence: 1b)

Gilron I, Watson CP, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. *CMAJ*. 2006;175:265-75.

We propose a primary care algorithm for treatments with the most favourable risk-benefit profile, including topical lidocaine, gabapentin, pregabalin, tricyclic antidepressants, mixed serotonin-norepinephrine reuptake inhibitors, tramadol and opioids.

PMID: 16880448

Rating: 5b

Gilron I, Coderre TJ. Emerging drugs in neuropathic pain. *Expert Opin Emerg Drugs*. 2007;12:113-26.

In the interest of improving patient care, the authors recommend implementing comparative studies throughout the development process in order to demonstrate the increased value of novel agents.

PMID: 17355217

Rating: 5b

Gimbel J, Linn R, Hale M, Nicholson B. Lidocaine patch treatment in patients with low back pain: results of an open-label, nonrandomized pilot study. *Am J Ther*. 2005;12:311-9.

Significant improvements in pain interference with quality of life (QOL) were noted for all BPI.

PMID: 16041194

Rating 4c

A non-controlled study of six-weeks in duration of patients with axial low back pain (ranging from acute/subacute to chronic), normal neurological exam, and no more than one spinal surgery was performed by the manufacturer of lidocaine patches. Patients with chronic pain were required to have diagnoses of internal disk disruption, spinal stenosis, spondylolisthesis or facet arthropathy. The Neuropathic Pain Scale was not used for an outcome. A large number of patients dropped out of this study (40/131) with 13.7% complaining of adverse effects (skin reactions, dizziness/lightheadedness, and headache) and 11% complaining of lack of efficacy. Overall at six weeks, 54% of patients reported moderate to complete improvement from baseline. The results also showed end-of-treatment reductions in an 11-point pain intensity rating scale of 21% for the short-term chronic and 32% for the long-term chronic low-back pain subgroups (≥ 30% is suggested as a clinically important reduction).The acute group had a 40% reduction, and the authors note that improvement could be secondary to spontaneous recovery.

Gitlow S, Barthwell A. Marijuana Is Not Medicine. American Society of Addiction Medicine (ASAM) 44th Annual Medical-Scientific Conference. Press Conference. Presented April 25, 2013.

Rating: 10b

Göbel H, Heinze A, Reichel G, Hefter H, Benecke R; Dysport myofascial pain study group. Efficacy and safety of a single botulinum type A toxin complex treatment (Dysport) for the relief of upper back myofascial pain syndrome: results from a randomized double-blind placebo-controlled multicentre study. *Pain*. 2006 Nov;125(1-2):82-8.

In conclusion, in patients with upper back myofascial pain syndrome, injections of 400 Ipsen units of Dysport at 10 individualised trigger points significantly improved pain levels 4-6 weeks after treatment.

PMID: 16750294

Rating: 2c

Goebel A, Barker CH, Turner-Stokes L, et al. Complex regional pain syndrome in adults: UK guidelines for diagnosis, referral and management in primary and secondary care. London: RCP, 2012.

Guidelines for treatment of CRPS compiled by the UK Royal College of Physicians.

Rating: 8a

Gold BD, Scheiman JM, Sabesin SM, Vitat P. Updates on the management of upper gastrointestinal disorders in the primary care setting: NSAID-related gastropathies and pediatric reflux diseases. *J Fam Pract*. 2007;56:S1-S12.

The use of "traditional" NSAIDs results in serious upper gastrointestinal (GI) adverse events in nearly one fourth of patients. Cyclooxygenase-2 (COX-2)-selective inhibitors are beneficial in alleviating GI adverse events, but with the possible trade-off of causing CV adverse events in at-risk patients.

PMID: 17343806

Rating: 5a

Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA*. 2004 Nov 17;292(19):2388-95.

The study concluded, “current evidence suggests efficacy of low-dose tricyclic antidepressants, cardiovascular exercise, cognitive behavioral therapy, and patient education. A number of other commonly used FMS therapies, such as trigger point injections, have not been adequately evaluated. Despite the chronicity and complexity of FMS, there are pharmacological and nonpharmacological interventions available that have clinical benefit. Based on current evidence, a stepwise program emphasizing education, certain medications, exercise, cognitive therapy, or all 4 should be recommended.”

PMID: 15547167

Rating: 1b

Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol*. 2007;2:499-511.

There is strong evidence that tricyclic antidepressants are effective, and moderate evidence for the effectiveness of serotonin reuptake inhibitors and dual serotonin-norepinephrine reuptake inhibitors.

PMID: 17602996

Rating: 5b

Goldberg RT; Pachas WN; Keith D. Relationship between traumatic events in childhood and chronic pain. *Disability Rehabilitation.* 01-Jan-1999; 21(1): 23-30.
Abstract:

CONCLUSIONS: Child traumatic events are significantly related to chronic pain.

PMID: 10070600

Publication Type: Case Control Study, 91 cases

Gore M, Dukes E, Rowbotham DJ, Tai KS, Leslie D. Clinical characteristics and pain management among patients with painful peripheral neuropathic disorders in general practice settings*. Eur J Pain*. 2007;11:652-64.

Among both Pure and Mixed PND patients, use and doses of evidenced-based neuropathic pain-related medications was low, and lower than the use of NSAIDs (a medication class with no proven efficacy for PNDs) in each group, suggesting possible sub-optimal neuropathic pain management among these patients.

PMID: 17126045

Rating: 4c

Gourlay GK, Cherry DA, Onley MM, Tordoff SG, Conn DA, Hood GM, Plummer JL. Pharmacokinetics and pharmacodynamics of twenty-four-hourly Kapanol compared to twelve-hourly MS Contin in the treatment of severe cancer pain. *Pain.* 1997;69:295-302.

PMID: 9085304

Rating: 1c

Graboski CL, Gray DS, Burnham RS. Botulinum toxin A versus bupivacaine trigger point injections for the treatment of myofascial pain syndrome: a randomised double blind crossover study. *Pain.* 2005 Nov;118(1-2):170-5. Epub 2005 Oct 3.

Glenrose Rehabilitation Hospital, 10230 111Ave, Edmonton Ab, T5G 0B7, Canada. cgraboski@shaw.ca

The purpose of this study was to compare the effectiveness of trigger point injections using BTX A versus bupivacaine, both in combination with a home-based rehabilitation program. Both treatments were effective in reducing pain when compared to baseline (P=0.0067). There was, however, no significant difference between the BTX A and 0.5% bupivacaine groups in duration or magnitude of pain relief, function, satisfaction or cost of care (cost of injectate excluded). Considering the high cost of BTX A, bupivacaine is deemed a more cost-effective injectate for MPS.

PMID: 16202527

Rating: 2c

Grabow TS, Guarino Ah, Raja SN. Complex regional pain syndromes: Diagnosis and treatment. In: Benzon HT, Raja SN, Molloy RE, Liu SS, Fishman SM. Essentials of Pain Medicine and Regional Anesthesia. 2nd ed. Elisevier, 2005.

Rating: 9a

Gradl G, Steinborn M, Wizgall I, Mittlmeier T, Schürmann M. Acute CRPS I (morbus sudeck) following distal radial fractures--methods for early diagnosis. *Zentralbl Chir.* 2003 Dec;128(12):1020-6.

PMID: 14750063

Rating: 4b

Graff-Radford SB. Myofascial pain: diagnosis and management. *Curr Pain Headache Rep*. 2004 Dec;8(6):463-7.

The therapy for myofascial pain requires enhancing central inhibition through pharmacology or behavioral techniques and simultaneously reducing peripheral inputs through physical therapies including exercises and trigger point-specific therapy.

PMID: 15509460

Rating: 5b

Gras-Miralles B, Cremonini F. A critical appraisal of lubiprostone in the treatment of chronic constipation in the elderly. *Clin Interv Aging*. 2013;8:191-200. doi: 10.2147/CIA.S30729.

PMID: 23439964

Rating: 5b

Grøndahl JR, Rosvold EO. Hypnosis as a treatment of chronic widespread pain in general practice: a randomized controlled pilot trial. *BMC Musculoskelet Disord*. 2008 Sep 18;9:124.

CONCLUSION: The study indicates that hypnosis treatment may have a positive effect on pain and quality of life for patients with chronic muscular pain. Considering the limited number of patients, more studies should be conducted to confirm the results.

PMID: 18801190

Rating: 2c

Gross DP, Battie MC. Predicting timely recovery and recurrence following multidisciplinary rehabilitation in patients with compensated low back pain. *Spine.* 2005 Jan 15;30(2):235-40.

RESULTS: The number of preadmission healthcare visits was the most robust predictor of all recovery outcomes. Recurrence rates were 18% in 1999 and 22% in 2000. A higher number of preadmission healthcare visits and more previous back-related claims were associated with higher risk of recurrence.

PMID: 15644763

Rating: 3b

Guay DR. Oxcarbazepine, topiramate, zonisamide, and levetiracetam: potential use in neuropathic pain. *Am J Geriatr Pharmacother.* 2003 Sep;1(1):18-37.

CONCLUSIONS: The ultimate role of these agents in the therapeutic armamentarium against pain requires further research and experience. In the interim, these 4 agents should be used to treat neuropathic pain in the elderly only when carbamazepine, gabapentin, or lamotrigine cannot be used or when the response to the aforementioned agents is suboptimal.

PMID: 15555463

Rating: 1b

Guillaume D, Van Havenbergh A, Vloeberghs M, Vidal J, Roeste G. A clinical study of intrathecal baclofen using a programmable pump for intractable spasticity. Arch Phys *Med Rehabil*. 2005;86:2165-71.

CONCLUSIONS: ITB therapy using a programmable pump is clinically effective and well tolerated, despite a seemingly high level of adverse events, in patients with intractable spasticity of spinal or cerebral origin and may offer improvements in pain relief and function.

PMID: 16271565

Rating: 3b

Gürol Z, Hekimoğlu S, Demirdamar R, Sumnu M. Percutaneous absorption of ketoprofen. I. In vitro release and percutaneous absorption of ketoprofen from different ointment bases. *Pharm Acta Helv*. 1996;71:205-12.

Since the efficacy of an ointment depends on the type of ointment base and the concentration of the drug, four different bases (white petrolatum, cold cream, hydrophilic ointment and Carbopol 940 gel) were used at 1, 3, 5, 7 and 10% concentrations of KP to evaluate the effect of ointment base and concentration.

PMID: 8818309

Rating: 4b

Gusi N, Tomas-Carus P. Cost-utility of an 8-month aquatic training for women with fibromyalgia: a randomized controlled trial. *Arthritis Res Ther*. 2008 Feb 22;10(1):R24.

CONCLUSIONS: The addition of an aquatic exercise programme to the usual care for fibromyalgia in women, is cost-effective in terms of both health care costs and societal costs.

PMID: 18294367

Rating: 2c

Guzman J, Esmail R, Karjalainen K. et al. Multidisciplinary Rehabilitation for Chronic Low Back Pain: Systematic Review. *BMJ* 2001;322:1511-1516.

CONCLUSIONS: The reviewed trials provide evidence that intensive multidisciplinary biopsychosocial rehabilitation with functional restoration reduces pain and improves function in patients with chronic low back pain.

Publication Type: Systematic Review/Meta-Analysis

PMID: 11420271

Rating: 1b

Guzmán J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary bio-psycho-social rehabilitation for chronic low back pain. *Cochrane Database Syst Rev*. 2002;(1):CD000963

CONCLUSIONS: The reviewed trials provide evidence that intensive multidisciplinary bio-psycho-social rehabilitation with a functional restoration approach improves pain and function. Less intensive interventions did not show improvements in clinically relevant outcomes.

PMID: 11869581

Rating: This review has been withdrawn.

Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Bolona ER, Sideras K, Uraga MV, Erwin PJ, Montori VM. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc*. 2007;82:29-39.

CONCLUSION: Currently available evidence weakly supports the inference that testosterone use in men is not associated with important cardiovascular effects.

PMID: 17285783

Rating: 1a

Halas CJ. Eszopiclone. *Am J Health Syst Pharm*. 2006;63:41-8.

Dosage adjustment is necessary in patients with severe hepatic disease and in those receiving concomitant potent cytochrome P-450 isoenzyme 3A4 inhibitors. No dosage adjustment is required for patients with renal dysfunction.

PMID: 1637346

Rating: 5b

Haldorsen EM, Grasdal AL, Skouen JS, Risa AE, Kronholm K, Ursin H. Is there a right treatment for a particular patient group? Comparison of ordinary treatment, light multidisciplinary treatment, and extensive multidisciplinary treatment for long-term sick-listed employees with musculoskeletal pain. *Pain.* 2002 Jan;95(1-2):49-63.

A simple, standardized, screening instrument including only psychological and physiotherapeutic observations may be a useful clinical tool for allocating patients with musculoskeletal pain to the right level of treatment.

PMID: 11790467

Rating: 2a

Hale M, Upmalis D, Okamoto A, Lange C, Rauschkolb C. Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. *Curr Med Res Opin*. 2009 May;25(5):1095-104.

CONCLUSION: During this 90-day study, tapentadol IR was associated with improved gastrointestinal tolerability compared with oxycodone IR while providing similar pain relief.

PMID: 19301989

Rating: 2b

Hall A, Maher C, Latimer J, Ferreira M. The effectiveness of Tai Chi for chronic musculoskeletal pain conditions: a systematic review and meta-analysis. *Arthritis Rheum*. 2009 Jun 15;61(6):717-24.

CONCLUSION: These data suggest that Tai Chi has a small positive effect on pain and disability in people with arthritis.

PMID: 19479696

Rating: 1c

Halvorsen PA, Selmer R, Kristiansen IS. Different ways to describe the benefits of risk-reducing treatments: a randomized trial. *Ann Intern Med.* 2007 Jun 19;146(12):848-56.

CONCLUSIONS: Treatment effects expressed in terms of NNT yielded higher consent rates than did those expressed as equivalent postponements.

PMID: 17577004

Rating: 2a

The NNT is a useful and relatively simple tool for practicing evidence-based medicine. This calculation can be applied to intervention studies and reflects the number of additional patients who need to receive an intervention to prevent 1 additional outcome. In the current study, using NNT was superior to achieve participant consent vs explanations focused on the postponements of outcomes for either all patients treated or a small, select group of patients treated.

CONCLUSIONS: Further studies are certainly warranted to identify the clinical neuropathic syndromes that are most sensitive to buprenorphine treatment, and to compare buprenorphine with other opioids in head-to-head trials of neuropathic pain.

Hans G. Buprenorphine--a review of its role in neuropathic pain. J Opioid Manag. 2007;3:195-206. Review.

PMID: 17957979

Rating: 1b

Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med*. 2007 May-Jun;8(4):326-31.

This topical update reports recent progress in the international effort to develop a more accurate and valid diagnostic criteria for complex regional pain syndrome (CRPS).

PMID: 17610454

Rating: 5b

Harden RN, Oaklander AL, Burton AW, Perez RS, Richardson K, Swan M, Barthel J, Costa B, Graciosa JR, Bruehl S. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. *Pain Med*. 2013;14:180-229.

PMID: 23331950

Rating: 6c

Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, Lubenow T, Buvanendran A, Mackey S, Graciosa J, Mogilevski M, Ramsden C, Chont M, Vatine JJ. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. *Pain.* 2010;150:268-74.

PMID: 20493633

Rating: 3b

Harden RN. Objectification of the diagnostic criteria for CRPS. *Pain Med.* 2010;11:1212-5.

PMID: 20704669

Rating: 5c

Hardy J, Quinn S, Fazekas B, Plummer J, Eckermann S, Agar M, Spruyt O, Rowett D, Currow DC. Randomized, double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain. *J Clin Oncol.* 2012 Oct 10;30(29):3611-7. doi: 10.1200/JCO.2012.42.1081.

Ketamine does not have net clinical benefit when used as an adjunct to opioids and standard coanalgesics in cancer pain.

PMID: 22965960

Rating: 2b

Härkäpää K, Mellin G, Järvikoski A, Hurri H. A controlled study on the outcome of inpatient and outpatient treatment of low back pain. Part III. Long-term follow-up of pain, disability, and compliance. *Scand J Rehabil Med*. 1990;22:181-8.

Pain and disability had decreased significantly in the two treated groups up to the 3-month follow-up.

PMID: 214822

Rating: 2c

Harke H, Gretenkort P, Ladleif HU, Rahman S. Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability. A prospective clinical study. *Eur J Pain*. 2005 Aug;9(4):363-73.

CONCLUSIONS: As a result of permanent pain relief under long-term SCS combined with physiotherapy, the functional status and the quality of life could be significantly improved in sympathetically maintained CRPS I.

PMID: 15979016

Rating: 2b

Harley CB, Liu W, Blasco M, Vera E, Andrews WH, Briggs LA, Raffaele JM. A natural product telomerase activator as part of a health maintenance program. *Rejuvenation Res*. 2011 Feb;14(1):45-56.

Low nanomolar levels of TA-65® moderately activated telomerase in human keratinocytes.

PMID: 20822369

Rating: 4c

Haroutiunian S, Drennan DA, Lipman AG. Topical NSAID therapy for musculoskeletal pain. *Pain Med*. 2010;11:535-49.

In acute and chronic low back pain, widespread musculoskeletal pain, and in peripheral neuropathic pain syndromes, the current evidence does not support the use of topical NSAIDs.

PMID: 20210866

Rating: 1a

Hartrick CT, Kovan JP, Naismith P. Outcome prediction following sympathetic block for complex regional pain syndrome. *Pain Pract*. 2004;4:222-8.

While sympathetic blocks can be helpful in the reduction of mechanical allodynia, and thus the facilitation of physical and occupational therapy, ultimate response to a regime that includes medications is not predicted by sympathetic block alone.

PMID: 17173603

Rating: 4c

Hartrick C, Van Hove I, Stegmann JU, Oh C, Upmalis D. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. *Clin Ther*. 2009 Feb;31(2):260-71.

CONCLUSIONS: Tapentadol IR 50 and 75 mg were associated with analgesia that was noninferior to that provided by oxycodone HCl IR 10 mg. Tapentadol treatment was associated with improved gastrointestinal tolerability.

PMID: 19302899

Rating: 2b

Hasenbring M, Ulrich HW, Hartmann M, Soyka D. The efficacy of a risk factor-based cognitive behavioral intervention and electromyographic biofeedback in patients with acute sciatic pain. An attempt to prevent chronicity. *Spine.* 1999 Dec 1;24(23):2525-35.

CONCLUSIONS: Individually scheduled, risk factor-based cognitive behavior therapy could be a beneficial treatment modality, which can be offered, in addition to a medical treatment, to patients with acute sciatica and psychosocial high risk factors for chronicity.

PMID: 10626316

Rating: 2c

Hassenbusch SJ, Portenoy RK, Cousins M, Buchser E, Deer TR, Du Pen SL, Eisenach J, Follett KA, Hildebrand KR, Krames ES, Levy RM, Palmer PP, Rathmell JP, Rauck RL, Staats PS, Stearns L, Willis KD. Polyanalgesic Consensus Conference 2003: an update on the management of pain by intraspinal drug delivery-- report of an expert panel. *J Pain Symptom Manage*. 2004 Jun;27(6):540-63.

Intraspinal drug infusion using fully implantable pump and catheter systems is a safe and effective therapy for selected patients with chronic pain. Rapid changes have occurred in the science and practice of intraspinal infusion and a Polyanalgesic Consensus Conference 2003 was organized.

PMID: 15165652

Rating: 5b

Hassenbusch, S. Intrathecal Clonidine in the Treatment of Intractable Pain: A Phase I/II Study" *Pain Medicine*. 2002; Volume 3, Number 2: 85-91.

Rating: 2c

Quality: Low. Total Rating: 2.0. Comment: Does not meet inclusion criteria for evidence-based review.

Hasson D, Arnetz B, Jelveus L, Edelstam B. A randomized clinical trial of the treatment effects of massage compared to relaxation tape recordings on diffuse long-term pain. *Psychother Psychosom*. 2004 Jan-Feb;73(1):17-24.

CONCLUSION: Massage, but not mental relaxation, is beneficial in attenuating diffuse musculoskeletal symptoms. Beneficial effects were registered only during treatment. 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.

PMID: 14665792

Rating: 2b

Häuser W, Urrútia G, Tort S, Uçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev*. 2013 Jan 31;1:CD010292. doi: 10.1002/14651858.CD010292.

The SNRIs duloxetine and milnacipran provided a small incremental benefit over placebo in reducing pain.

PMID: 23440848

Rating: 1b

Hawley JS, Weiner WJ. Psychogenic dystonia and peripheral trauma. *Neurology*. 2011;77:496-502.

PMID: 21810699

Rating: 5b

Heacock C, Bauer MS. Tolerance and dependence risk with the use of carisoprodol. Am Fam Physician. 2004 Apr 1;69(7):1622-3.

PMID: 15086035

Rating: 11b

Hedges DW, Brown BL, Shwalb DA, Godfrey K, Larcher AM. The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: a meta-analysis of double-blind, placebo-controlled trials. *J Psychopharmacol*. 2007; 21:102-11.

Consistent with previous studies, selective serotonin reuptake inhibitors appear more effective than placebo for social anxiety disorder, with improvement extending into social and occupational function.

PMID: 16714326

Rating: 1b

Helin-Salmivaara A, Huttunen T, Gronroos JM, Klaukka T, Huupponen R. Risk of serious upper gastrointestinal events with concurrent use of NSAIDs and SSRIs: a case-control study in the general population*. Eur J Clin Pharmacol*. 2007;63:403-8.

The respective AOR for traditional, non-selective NSAIDs was 1.77 (95%CI: 1.31-2.38), for semi-selective NSAIDs (nimesulide, nabumetone, meloxicam, and etodolac) 1.30 (95%CI: 0.76-2.24) and for COX-2 selective NSAIDs 1.33 (95%CI: 0.70-2.50).

PMID: 17347805

Rating; 3a

In adults with antimuscarinic refractory neurogenic detrusor overactivity and multiple sclerosis onabotulinumtoxinA is well tolerated and provides clinically beneficial improvement for

Herschorn S, Gajewski J, Ethans K, Corcos J, Carlson K, Bailly G, Bard R, Valiquette L, Baverstock R, Carr L, Radomski S. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. *J Urol.* 2011 Jun;185(6):2229-35.
up to 9 months.

PMID: 21497851

Rating: 2b

Photoallergic contact dermatitis from ketoprofen-containing topical preparations usually includes severe eczematous reactions.

Hindsén M, Zimerson E, Bruze M. Photoallergic contact dermatitis from ketoprofen in southern Sweden. *Contact Dermatitis*. 2006;54:150-7.

PMID: 16524438

Rating: 5b

Ho KY, Tan KH. Botulinum toxin A for myofascial trigger point injection: A qualitative systematic review. *Eur J Pain*. 2007;11:519-27. 2006 Oct 26; [Epub ahead of print]

Pain Management Services, Department of Anaesthesia and Surgical Intensive Care, Singapore General Hospital, Outram Road, Singapore 169608, Singapore.

The current evidence does not support the use of BTA injection in trigger points for myofascial pain. The data is limited and clinically heterogeneous.

PMID: 17071119

Rating: 1a

Hoffman EJ, Mathew SJ. Anxiety disorders: a comprehensive review of pharmacotherapies. *Mt Sinai J Med*. 2008; 75:248-62.

There is evidence from multiple randomized, placebo-controlled trials to support the use of selective serotonin reuptake inhibitors as first-line pharmacotherapy in these disorders.

PMID: 18704983

Rating: 1a

Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ*. 2000 Jan 25;162(2):225-33.

INTERPRETATION: The use of benzodiazepines in the treatment of insomnia is associated with an increase in sleep duration, but this is countered by a number of adverse effects.

Rating: 1a

Holzer A, Leitgeb U, Spacek A, Wenzl R, Herkner H, Kettner S. Auricular acupuncture for postoperative pain after gynecological surgery: a randomized controlled trail. *Minerva Anestesiol*. 2011 Mar;77(3):298-304.

PMID: 21441884

Rating: 2b

Homik JE, Suarez-Almazor M. An economic approach to health care. *Best Pract Res Clin Rheumatol.* 2004 Apr;18(2):203-18.

Given the unanswered questions that still exist, it seems reasonable to conclude that COX-2 inhibitors may be cost effective when used in patients at a high risk of GI complications.

PMID: 15121040

Rating: 5b

Honig LS, Kang MS, Schupf N, Lee JH, Mayeux R. Association of Shorter Leukocyte Telomere Repeat Length With Dementia and Mortality. *Arch Neurol.* 2012 Jul 23:1-8. doi: 10.1001/archneurol.2012.1541.

Our findings suggest that shortened leukocyte TL is associated with risks for dementia and mortality and may therefore be a marker of biological aging.

PMID: 22825311

Rating: 3a

Hsu ES. Practical management of complex regional pain syndrome. *Am J Ther*. 2009;16:147-54.

PMID: 19300041

Rating: 5c

Hunt RH, Choquette D, Craig BN, De Angelis C, Habal F, Fulthorpe G, Stewart JI, Turpie AG, Davis P. Approach to managing musculoskeletal pain: acetaminophen, cyclooxygenase-2 inhibitors, or traditional NSAIDs? *Can Fam Physician*. 2007;53:1177-84.

Treatment should begin with an effective analgesic with the best safety profile at the lowest dose and escalate to higher doses and different analgesics as required. Acetaminophen is a safe medication that should be considered first-line therapy.

PMID: 17872814

Rating: 5b

Institute for Clinical Systems Improvement (ICSI). Assessment and management of chronic pain. Bloomington (MN). 2005 Nov.

The goals of treatment are an emphasis on improving function through the development of long =-term self-management skills including fitness and a healthy lifestyle.

Rating: 6a

Institute for Clinical Systems Improvement (ICSI). Assessment and management of chronic pain (2nd edition). Bloomington (MN). 2007 Mar.

Skeletal muscle relaxants were found to have limited evidence of effectiveness. They were thought to be useful for short-term management of muscle spasm and pain. Mixed evidence was found for long-term use.

Rating: 6a

Institute for Clinical Systems Improvement (ICSI). Assessment and management of chronic pain (4nd edition). Bloomington (MN). 2009.

The 4th edition of this guideline addresses evaluation and treatment of chronic pain with a strong emphasis on comprehensive care.

Rating: 6a

International Research Foundation for RSD/CRPS. Reflex sympathetic dystrophy/complex regional pain syndrome. 3rd ed. Tampa (FL): International Research Foundation for RSD/CRPS; 2003. Retrieved July 2008.

No abstract available. A consensus guideline for diagnosis and treatment of CRPS.

Rating: 5b

Ipser JC, Kariuki CM, Stein DJ. Pharmacotherapy for social anxiety disorder: a systematic review. *Expert Rev Neurother*. 2008; 8:235-57.

Taken together, trials of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors provide the largest evidence base for agents that are both effective and well tolerated.

PMID: 18271710

Rating: 1a

Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Bonifacio V, Aversa A, Isidori A, Fabbri A, Lenzi A. Clin Endocrinol (Oxf). 2005 Dec;63(6):601-2. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol* (Oxf). 2005;63:381-94.

The evidence for a beneficial effect of T treatment on erectile function should be tempered with the caveats that the effect tends to decline over time, is progressively smaller with increasing baseline T levels, and long-term safety data are not available.

PMID: 16181230

Rating: 1a

Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, Lenzi A, Fabbri A. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol* (Oxf). 2005;63:280-93.

CONCLUSION: Our findings are sufficiently strong to justify further interventional studies focused on alternative targets of androgenic treatment carrying more stringent clinical implications, in particular the cardiovascular, metabolic and neurological systems.

PMID: 16117815

Rating: 1a

Jabbari B, Ney J, Sichani A, Monacci W, Foster L, Difazio M. Treatment of refractory, chronic low back pain with botulinum neurotoxin A: an open-label, pilot study. *Pain Med.* 2006 May-Jun;7(3):260-4.

CONCLUSION: Botulinum neurotoxin A may be beneficial in patients with chronic low back pain. A favorable initial response predicts subsequent responsiveness.

PMID: 16712627

Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA. 2012 Apr 25;307(16):1736-45. doi: 10.1001/jama.2012.505.

Botulinum toxin A compared with placebo was associated with a small to modest benefit for chronic daily headaches and chronic migraines but was not associated with fewer episodic migraine or chronic tension-type headaches per month.

Rating: 1a

Jänig W, Baron R. Experimental approach to CRPS. *Pain*. 2004;108:3-7.

PMID: 15109501

Rating: 5c

A review discussing the potential role of immobilization in CRPS.

Jensen TS, Backonja MM, Hernández Jiménez S, Tesfaye S, Valensi P, Ziegler D. New perspectives on the management of diabetic peripheral neuropathic pain. *Diab Vasc Dis Res*. 2006;3:108-19.

Addition of an opioid agonist may be required in the event of inadequate pain control. Irrespective of which treatment is offered, only about one third of patients are likely to achieve more than 50% pain relief.

PMID: 17058631

Rating: 5b

Jensen MP, Ehde DM, Gertz KJ, Stoelb BL, Dillworth TM, Hirsh AT, Molton IR, Kraft GH. Effects of self-hypnosis training and cognitive restructuring on daily pain intensity and catastrophizing in individuals with multiple sclerosis and chronic pain. *Int J Clin Exp Hypn*. 2011 Jan;59(1):45-63.

The findings supported the greater beneficial effects of HYP, relative to CR, on average pain intensity. The CR-HYP treatment appeared to have beneficial effects greater than the effects of CR and HYP alone.

PMID: 21104484

Rating: 2c

Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA*. 2004 Jul 21;292(3):338-43.

"The risk of suicidal behavior after starting antidepressant treatment is similar among users of amitriptyline, fluoxetine, and paroxetine compared with the risk among users of dothiepin."

PMID: 15265848

Rating: 4a

Johnsen SP, Larsson H, Tarone RE, McLaughlin JK, Norgard B, Friis S, Sorensen HT. Risk of hospitalization for myocardial infarction among users of rofecoxib, celecoxib, and other NSAIDs: a population-based case-control study. *Arch Intern Med.* 2005 May 9;165(9):978-84.

CONCLUSIONS: Current and new users of all classes of nonaspirin NSAIDs had elevated relative risk estimates for MI.

PMID: 15883235

Rating: 4a

Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: A meta-analysis of randomized controlled trials. *Pain*. 2007 Jul;130(1-2):157-65. Epub 2007 Mar 23.

PMID: 17383095

Rating: 1c

This meta-analysis came to the conclusion that electrical nerve stimulation (ENS) provided a significant decrease in chronic pain. 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 were included as "mechanism, rather than anatomic location of pain, is likely to be a critical factor for therapy." This study was funded by Empi, Inc. and performed by an independent contractor, Princeton Reimbursement Group. This group provides consulting services to medical technology companies to address reimbursement issues.

CONCLUSIONS: This study suggests that early tertiary nonoperative care, once patients with chronic spinal disorders are identified as having potentially high-cost chronic pain and disability,

Jordan KD, Mayer TG, Gatchel RJ. Should extended disability be an exclusion criterion for tertiary rehabilitation? Socioeconomic outcomes of early versus late functional restoration in compensation spinal disorders. *Spine.* 1998 Oct 1;23(19):2110-6; discussion 2117.
is efficacious in achieving goals of better work return and work retention.

PMID: 9794056

Rating: 3a

Kahan M, Srivastava A, Wilson L, Gourlay D, Midmer D. Misuse of and dependence on opioids: study of chronic pain patients*. Can Fam Physician*. 2006;52:1081-7.

PMID: 17279218

Rating 5b

Kalyani RR, Stein B, Valiyil R, Manno R, Maynard JW, Crews DC. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. *J Am Geriatr Soc*. 2010 Jul;58(7):1299-310. Epub 2010 Jun 23.

CONCLUSION: Vitamin D treatment effectively reduces the risk of falls in older adults.

PMID: 20579169

Rating: 1b

Kamanli A, Kaya A, Ardicoglu O, Ozgocmen S, Zengin FO, Bayik Y. Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome. *Rheumatol Int*. 2005 Oct;25(8):604-11. Epub 2004 Sep 15.

Division of Rheumatology, Department of Physical Medicine and Rehabilitation, Firat University, Elazig, Turkey. akamanli@hotmail.com

CONCLUSIONS: Injection is more practical and rapid, since it causes less disturbance than dry needling and is more cost effective than BTX-A injection, and seems the treatment of choice in MPS. On the other hand, BTX-A could be selectively used in MPS patients resistant to conventional treatments.

PMID: 15372199

Rating: 2c

Kapczinski F, Lima MS, Souza JS, Schmitt R. Antidepressants for generalized anxiety disorder. *Cochrane Database Syst Rev*. 2003;(2):CD003592.

CONCLUSIONS: The available evidence suggests that antidepressants are superior to placebo in treating GAD.

PMID: 12804478

Rating: 1c

Karjalainen K, Malmivaara A, van Tulder M, Roine R, Jauhiainen M, Hurri H, Koes B. Multidisciplinary biopsychosocial rehabilitation for neck and shoulder pain among working age adults. *Cochrane Database Syst Rev*. 2003;(2):CD002194.

CONCLUSIONS: We conclude that there appears to be little scientific evidence for the effectiveness of multidisciplinary biopsychosocial rehabilitation compared with other rehabilitation facilities for neck and shoulder pain.

PMID: 12804428

Rating: 1c

Katz J, Pennella-Vaughan J, Hetzel RD, Kanazi GE, Dworkin RH. A randomized, placebo-controlled trial of bupropion sustained release in chronic low back pain. *J Pain.* 2005 Oct;6(10):656-61.

Antidepressant medications that have both noradrenergic and serotonergic effects appear to have greater efficacy in patients with chronic low back pain than those with only serotonergic activity. We studied bupropion because it inhibits the reuptake of both norepinephrine and dopamine, but found no evidence of efficacy in patients with non-neuropathic chronic low back pain.

PMID: 16202958

Rating: 2c

Keefe FJ, Block AR, Williams RB Jr, Surwit RS. Behavioral treatment of chronic low back pain: clinical outcome and individual differences in pain relief. *Pain*. 1981 Oct;11(2):221-31.

PMID: 6459557

Rating: 4b

Keel PJ, Wittig R, Deutschmann R, Diethelm U, Knüsel O, Löschmann C, Matathia R, Rudolf T, Spring H. Effectiveness of in-patient rehabilitation for sub-chronic and chronic low back pain by an integrative group treatment program (Swiss Multicentre Study). *Scand J Rehabil Med*. 1998 Dec;30(4):211-9.

The main conclusion is that an integrated approach promoting self control and behaviour change through educational measures achieves better long-term results than the traditional individual physiotherapy approach.

PMID: 9825385

Rating: 3b

Keitel W, Frerick H, Kuhn U, Schmidt U, Kuhlmann M, Bredehorst A. Capsicum pain plaster in chronic non-specific low back pain. *Arzneimittelforschung*. 2001 Nov;51(11):896-903.

As in comparably positive randomised studies with capsaicin cream in patients with osteoarthritis or fibromyalgia it was shown that a capsicum plaster preparation can also be used to advantage in chronic non-specific back pain.

PMID: 11765591

Rating: 2b

Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, van den Wildenberg FA, Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy, *N Engl J Med*. 2000 Aug 31;343(9):618-24.

RESULTS: The proportion of patients with a score of 6 ("much improved") for the global perceived effect was much higher in the spinal cord stimulation group than in the control group (39 percent vs. 6 percent, P=0.01). There was no clinically important improvement in functional status. The health-related quality of life improved only in the 24 patients who actually underwent implantation of a spinal cord stimulator. Six of the 24 patients had complications that required additional procedures, including removal of the device in 1 patient.

PMID: 10965008

Rating: 2c

Kemler MA, Furnee CA, Economic evaluation of spinal cord stimulation for chronic reflex sympathetic dystrophy, *Neurology.* 2002 Oct 22;59(8):1203-9

CONCLUSIONS: The authors found SCS to be both more effective and less expensive as compared with the standard treatment protocol for chronic RSD.

PMID: 12391348

Rating: 2c

Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med*. 2000 Aug 31;343(9):618-24.

CONCLUSIONS: In carefully selected patients with chronic reflex sympathetic dystrophy, electrical stimulation of the spinal cord can reduce pain and improve the health-related quality of life.

PMID: 10965008

Rating: 2c

Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol.* 2004 Jan;55(1):13-8.

After careful selection and successful test stimulation, spinal cord stimulation results in a long-term pain reduction and health-related quality of life improvement in chronic reflex sympathetic dystrophy.

PMID: 14705107

Rating: 2b

Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. *J Neurosurg*. 2008 Feb;108(2):292-8.

CONCLUSIONS: Despite the diminishing effectiveness of SCS over time, 95% of patients with an implant would repeat the treatment for the same result.

PMID: 18240925

Rating: 2b

The main analysis showed that change in pain intensity was not significantly different between the SCS plus phyisician therapy group and the phyisician therapy alone group (p=0.25)..

Kerns RD, Thorn BE, Dixon KE. Psychological treatments for persistent pain: An introduction. *J Clin Psychol*. 2006 Aug 25; [Epub ahead of print]

Psychological treatments for persistent pain have been demonstrated to be effective alternatives or adjuncts to more traditional methods for promoting optimal pain management.

PMID: 16937343

Rating: 5a

Khaliq W, Alam S, Puri N. Topical lidocaine for the treatment of postherpetic neuralgia. *Cochrane Database Syst Rev*. 2007; 18:CD004846.

CONCLUSIONS: There is insufficient evidence to recommend topical lidocaine as a first-line agent in the treatment of postherpetic neuralgia with allodynia.

PMID: 17443559

Rating: 1c

Kienzler JL, Gold M, Nollevaux F. Systemic bioavailability of topical diclofenac sodium gel 1% versus oral diclofenac sodium in healthy volunteers. *J Clin Pharmacol*. 2010;50:50-61.

Topical diclofenac did not inhibit platelet aggregation and inhibited COX-1 and COX-2 less than oral diclofenac.

PMID: 19841157

Rating: 2c

This study was sponsored by Novartis

Knotkova H, Pappagallo M. Adjuvant analgesics. *Med Clin North Am*. 2007;91:113-24.

Moderate to severe pain/functional impairment; pain with a score of >4 on the brief pain inventory. 1. Gabapentinoid (gabapentin, pregabalin)+/-Opioid/opioid rotation or 2. Antidepressant (TCA, duloxetine, venlafaxine)+/-Opioid/opioid rotation or 3. Gabapentinoid+antidepressant+Opioid/opioid rotation.

PMID: 17164107

Rating: 5b

Koke AJ, Schouten JS, Lamerichs-Geelen MJ, Lipsch JS, Waltje EM, van Kleef M, Patijn J. Pain reducing effect of three types of transcutaneous electrical nerve stimulation in patients with chronic pain: a randomized crossover trial. *Pain.* 2004;108:36-42.

We concluded that there were no differences in effectiveness for the three types of TENS used in this study.

PMID: 15109505

Rating: 2c

Kokkonen H, Söderström I, Rocklöv J, Hallmans G, Lejon K, Rantapää Dahlqvist S. Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. *Arthritis Rheum*. 2010 Feb;62(2):383-91.

CONCLUSION: Individuals in whom RA later developed had significantly increased levels of several cytokines.

PMID: 20112361

Rating: 4b

Kool J, Bachmann S, Oesch P, Knuesel O, Ambergen T, de Bie R, van den Brandt P. Function-centered rehabilitation increases work days in patients with nonacute nonspecific low back pain: 1-year results from a randomized controlled trial. *Arch Phys Med Rehabil*. 2007 Sep;88(9):1089-94.

CONCLUSIONS: FCT is more effective than PCT for increasing work days.

PMID: 17826451

Rating: 2b

Kool JP, Oesch PR, Bachmann S, Knuesel O, Dierkes JG, Russo M, de Bie RA, van den Brandt PA. Increasing days at work using function-centered rehabilitation in nonacute nonspecific low back pain: a randomized controlled trial. *Arch Phys Med Rehabil*. 2005 May;86(5):857-64.

Function-centered rehabilitation increases the number of work days, self-efficacy, and lifting capacity in patients with nonacute nonspecific LBP.

PMID: 15895328

Rating: 2b

When compared with absorption characteristics of diclofenac potassium 50-mg tablet, DPSGC was more rapidly and consistently absorbed after bunionectomy. These characteristics should

Kowalski M, Stoker DG, Bon C, Moore KA, Boesing SE. A Pharmacokinetic Analysis of Diclofenac Potassium Soft-Gelatin Capsule in Patients After Bunionectomy. *Am J Ther*. 2009 Jun 13.
be advantageous when rapid pain relief is desired.

PMID: 19531931

Rating: 2c

Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med*. 2009;150:387-95.

Clinicians should inform patients of arrhythmia risk when they prescribe methadone.

PMID: 19153406

Rating: 8b

While attempting to solidify a guide for pre-treatment EKGs with use of methadone, this article was extremely controversial, with multiple letters written. Concern was even made over the significance of cardiac pathology with use. It would appear that there should be a very high tolerance for the use of EKGs based on the literature gathered.

Krause N, Ragland DR. Occupational disability due to low back pain: a new interdisciplinary classification based on a phase model of disability. *Spine*. 1994;19:1011-20

The proposed eight-phase classification is based primarily on the presence and duration of work-disability rather than on clinical categories.

PMID: 8029734

Rating: 5b

Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2012;2:e000850 doi:10.1136/bmjopen-2012-000850.

Receiving hypnotic prescriptions was associated with greater than threefold increased hazards of death even when prescribed <18 pills/year. This association held in separate analyses for several commonly used hypnotics and for newer shorter-acting drugs. Control of selective prescription of hypnotics for patients in poor health did not explain the observed excess mortality.

Rating: 3a

Kröner-Herwig B. Chronic pain syndromes and their treatment by psychological interventions. *Curr Opin Psychiatry*. 2009 Mar;22(2):200-4.

FINDINGS: Several reviews on systematic research studies confirm that psychological interventions are efficacious in the treatment of chronic musculoskeletal pain, especially back pain, though effect sizes are small and, in some cases, moderate.

PMID: 19553876

Rating: 1a

Krummel T, Dimitrov Y, Moulin B, Hannedouche T. Drug points: Acute renal failure induced by topical ketoprofen. *BMJ*. 2000;320:93.

PMID: 10625264

Case study of renal failure.

Rating: 5c

Krumova EK, Gussone C, Regeniter S, Westermann A, Zenz M, Maier C. Are sympathetic blocks useful for diagnostic purposes? *Reg Anesth Pain Med*. 2011;36:560-7.

PMID: 21941221

Rating: 5b

Krumova EK, Frettlöh J, Klauenberg S, Richter H, Wasner G, Maier C. Long-term skin temperature measurements - a practical diagnostic tool in complex regional pain syndrome. *Pain*. 2008;140:8-22.

PMID: 18723287

Rating; 5c

Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. *Curr Psychiatry Rep*. 2010 Oct;12(5):448-53.

Long-acting, sustained-release formulations (injectable and implantable) seem particularly effective compared with oral formulations.

PMID: 20640538

Rating: 1b

Krupitsky E. Continued Naltrexone Use Prevents Opioid Dependency Relapse. 24th Annual US Psychiatric and Mental Health Congress in Las Vegas, Nevada. November 10, 2011.

Continued use of once-monthly extended-release naltrexone (NTX) intramuscular injection (Vivitrol) is a safe and effective method of preventing relapse to opioid dependency after detoxification. It significantly increased the number of abstinence weeks (90% vs 35% for placebo) and the likelihood of total abstinence (36% vs 23).

Rating: 10b

Kuffner EK, Green JL, Bogdan GM, Knox PC, Palmer RB, Heard K, Slattery JT, Dart RC. The effect of acetaminophen (four grams a day for three consecutive days) on hepatic tests in alcoholic patients--a multicenter randomized study. *BMC Med.* 2007;5:13.

CONCLUSION: Alcoholic patients treated with the maximum recommended daily dose of acetaminophen for 3 consecutive days did not develop increases in serum transaminase or other measures of liver injury. Treatment of pain or fever for 3 days with acetaminophen appears safe in newly-abstinent alcoholic patients, such as those presenting for acute medical care.

PMID: 17537264

Rating; 2a

Kumar D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. *Diabetes Care*. 1997 Nov;20(11):1702-5.

PMID: 9353612

Rating: 2c

Kumar D, Alvaro MS, Julka IS, Marshall HJ. Diabetic peripheral neuropathy. Effectiveness of electrotherapy and amitriptyline for symptomatic relief. *Diabetes Care*. 1998 Aug;21(8):1322-5.

PMID: 9702441

Rating: 2c

Kumar K, Malik S, Demeria D, Treatment of chronic pain with spinal cord stimulation versus alternative therapies: cost-effectiveness analysis, Neurosurgery. 2002 Jul;51(1):106-15; discussion 115-6.

CONCLUSION: SCS is cost-effective in the long term, despite the initial high costs of the implantable devices.

PMID: 12182407

Rating: 3b

Kumar K, Hunter G, Demeria DD. Treatment of chronic pain by using intrathecal drug therapy compared with conventional pain therapies: a cost-effectiveness analysis. *J Neurosurg*. 2002 Oct;97(4):803-10.

The Oswestry Disability Index showed a 27% improvement for patients in the IDT group, compared with a 12% improvement in the control group.

PMID: 12405366

Rating: 3b

Kumar R. Approved and investigational uses of modafinil: an evidence-based review. *Drugs*. 2008;68(13):1803-39.

PMID: 18729534

Rating: 5b

Kuna ST, Gurubhagavatula I, Maislin G, Hin S, Hartwig KC, McCloskey S, Hachadoorian R, Hurley S, Gupta R, Staley B, Atwood CW. Noninferiority of functional outcome in ambulatory management of obstructive sleep apnea. *Am J Respir Crit Care Med.* 2011 May 1;183(9):1238-44. doi: 10.1164/rccm.201011-1770OC.

PMID: 21471093

Rating: 3b

Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. *CNS Drugs*. 2009;23:19-34.

PMID: 19062773

Rating: 5a

Laine L, Curtis SP, Cryer B, Kaur A, Cannon CP; MEDAL Steering Committee. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison*. Lancet*. 2007; 369:465-73.

There were significantly fewer upper gastrointestinal clinical events with the COX-2 selective inhibitor etoricoxib than with the traditional NSAID diclofenac due to a decrease in uncomplicated events, but not in the more serious complicated events.

PMID: 17292766

Rating: 3a

Laine L. GI risk and risk factors of NSAIDs. *J Cardiovasc Pharmacol*. 2006;47 Suppl 1:S60-6.

The decision to employ a protective strategy to decrease NSAID-associated GI clinical events is based on risk stratification. Strategies employed include the use of non-NSAID analgesics, use of lowest effective dose of NSAID, use of medical cotherapy (eg, proton pump inhibitor, misoprostol), or use of coxibs.

PMID: 16785831

Rating: 5c

Laine L, White WB, Rostom A, Hochberg M. COX-2 Selective Inhibitors in the Treatment of Osteoarthritis. *Semin Arthritis Rheum*. 2008 Jan 3 [Epub ahead of print].

Meta-analysis of randomized trials indicates that coxibs increase the risk of myocardial infarctions approximately twofold versus placebo and versus naproxen, but do not increase the risk versus nonnaproxen NSAIDs.

PMID: 18177922

Rating: 1b

Laine L, White WB, Rostom A, Hochberg M. COX-2 Selective Inhibitors in the Treatment of Osteoarthritis. *Semin Arthritis Rheum*. 2008 Jan 3. [Epub ahead of print]

CONCLUSIONS: Coxibs are as effective as traditional NSAIDs and superior to acetaminophen for the treatment of OA.

PMID: 18177922

Rating: 5a

This article contains a nice review of the associated side effects of acetaminophen in comparison to NSAIDs

Lake AE 3rd. Screening and behavioral management: medication overuse headache--the complex case. *Headache*. 2008;48:26-31.

Daily use of opioids for other medical conditions, psychiatric comorbidity including borderline personality disorder, prior history of other substance dependence or abuse, and family history of substance disorders are risk factors for MOH.

PMID: 18184282

Rating 5c

Lanas A, Hunt R. Prevention of anti-inflammatory drug-induced gastrointestinal damage: benefits and risks of therapeutic strategies. *Ann Med*. 2006;38:415-28.

PPI therapy must be considered for the treatment and prevention of NSAID-induced dyspepsia.

PMID: 17008305

Rating: 5b

Landy S, Altman CA, Xie F. Time to recovery in patients with acute painful musculoskeletal conditions treated with extended-release or immediate-release cyclobenzaprine. *Adv Ther*. 2011 Mar 18. [Epub ahead of print]

RESULTS: A total of 504 patients were randomized. Median times to "very good" or "excellent" medication helpfulness were 10 days for extended release, and 7 days for immediate release versus over 14 days for placebo.

PMID: 21424735

Rating: 2b

Lang AE, Chen R. Dystonia in complex regional pain syndrome type I. *Ann Neurol*. 2010;67:412-4.

PMID: 20373359

An unstructured review discussing the pathogenesis of dystonia in CRPS including the possibility of that this is psychogenic.

Rating: 5c

Lange B, Kuperwasser B, Okamoto A, Steup A, Häufel T, Ashworth J, Etropolski M. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv Ther*. 2010 Jun;27(6):381-99. Epub 2010 Jun 11.

Tapentadol was efficacious and provided efficacy that was similar to oxycodone for the management of chronic osteoarthritis knee and low back pain, with a superior gastrointestinal tolerability profile and fewer treatment discontinuations.

PMID: 20556560

Rating: 2a

Lange G, Janal MN, Maniker A, Fitzgibbons J, Fobler M, Cook D, Natelson BH. Safety and Efficacy of Vagus Nerve Stimulation in Fibromyalgia: A Phase I/II Proof of Concept Trial. *Pain Med*. 2011 Sep;12(9):1406-1413. Epub 2011 Aug 3.

Preliminary outcome measures suggested that VNS may be a useful adjunct treatment for FM patients resistant to conventional therapeutic management, but further research is required to better understand its actual role in the treatment of FM.

PMID: 21812908

Rating: 4c

Lasco A, Catalano A, Benvenga S. Improvement of Primary Dysmenorrhea Caused by a Single Oral Dose of Vitamin D: Results of a Randomized, Double-blind, Placebo-Controlled Study. *Arch Intern Med.* 2012;172(4):366-367. doi:10.1001/archinternmed.2011.715

The study included 40 women aged 18 to 40 years who had experienced at least 4 consecutive painful menstrual periods in the past 6 months and had a 25(OH)D serum level below the upper limit of the lowest quartile (<45 ng/mL). They were not taking calcium, vitamin D, oral contraceptives, or other medications, and they had not used an intrauterine contraceptive device during the previous 6 months.

PMID: 22371927

Rating: 2b

Lechat P, Slanar O. Ketoprofen Topical. European Medicines Agency. 2010.

This is a discussion of the use of topical ketoprofen, including risk-benefit in Europe.

Rating: 8a

Lederman S, Moldofsky H, Harris HW, Archambault WT, Kwong T. Effects of Bedtime Very Low Dose Cyclobenzaprine on Symptoms and Sleep Physiology in Patients with Fibromyalgia Syndrome: A Double-blind Randomized Placebo-controlled Study. *J Rheumatol.* 2011 Sep 1. [Epub ahead of print]

CONCLUSION: Bedtime VLD CBP treatment improved core FM symptoms.

PMID: 21885490

Rating: 2c

Lee DC. Sedative Hypnotic Agents. In: Goldfrank's Toxicological Emergencies, 7th ed. 2002. McGraw-Hill.

Rating: 9b

Lee MS, Pittler MH, Ernst E. Internal Qigong for Pain Conditions: A Systematic Review. *J Pain*. 2009 Jun 24. [Epub ahead of print]

This review of controlled clinical trials focused on the effects of internal qigong, a self-directed energy healing intervention involving movement and meditation. Collectively, the existing trial evidence is not convincing enough to suggest that internal qigong is an effective modality for pain management.

PMID: 19559656

Rating: 1c

Lee GW, Weeks PM. The role of bone scintigraphy in diagnosing reflex sympathetic dystrophy. *J Hand Surg Am.* 1995 May;20(3):458-63.

PMID: 7642927

Rating: 5b

Levendoglu F, Ogun CO, Ozerbil O, Ogun TC, Ugurlu H, Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury, *Spine*. 2004 Apr 16;29(7):743-51.

CONCLUSIONS: Gabapentin can be added to the list of first-line medications for the treatment of chronic neuropathic pain in spinal cord injury patients. It is a promising new agent and offers advantages over currently available treatments.

PMID: 15087796

Rating: 2b

Levran O, Yuferov V, Kreek MJ. The genetics of the opioid system and specific drug addictions. *Hum Genet.* 2012;131:823-42.

In this review, we will describe the genetics of the major genes of the opioid system (opioid receptors and their endogenous ligands) in connection to addiction to opioids, cocaine, alcohol and methamphetamines. Particular emphasis is given to association and functional studies of specific variants.

PMID: 22547174

Rating: 1a

***Lexi-Comp Inc*. Lexi-Drugs Online™ , Hudson, Ohio: Lexi-Comp, Inc. 2008.**

Rating: 9a

Li Z, Smith BP, Smith TL, Koman LA. Diagnosis and management of complex regional pain syndrome complicating upper extremity recovery. J Hand Ther. 2005 Apr-Jun;18(2):270-6.

CRPS is common after hand trauma or surgery. Patient-specific hand therapy is very important in reducing swelling, decreasing pain, and improving range of motion.

PMID: 15891984

Rating: 5b

Liebrenz M, Boesch L, Stohler R, Caflisch C. Agonist substitution--a treatment alternative for high-dose benzodiazepine-dependent patients? *Addiction*. 2010;105:1870-4.

PMID: 20456294

Rating: 11a

Lin EH, Katon W, Von Korff M, Tang L, Williams JW Jr, Kroenke K, Hunkeler E, Harpole L, Hegel M, Arean P, Hoffing M, Della Penna R, Langston C, Unutzer J; IMPACT Investigators. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA*. 2003 Nov 12;290(18):2428-9.

The conclusion was, “In a large and diverse population of older adults with arthritis (mostly osteoarthritis) and comorbid depression, benefits of improved depression care extended beyond reduced depressive symptoms and included decreased pain as well as improved functional status and quality of life.”

PMID: 14612479

Rating: 2a

Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ*. 2004 Aug 7;329(7461):324.

CONCLUSION: No trial data support the long-term use of topical NSAIDs in osteoarthritis.

PMID: 15286056

Rating: 1b

Lingford-Hughes AR, Welch S, Nutt DJ; British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2004 Sep;18:293-335.

PMID: 15358975

Rating: 8a

Linton SJ. Early identification and intervention in the prevention of musculoskeletal pain. *American Journal of Independent Medicine*. 2002 May.

Conclusions: It appears to be feasible to identify patients with high levels of risk and to subsequently lower the risk for work disability by administering a cognitive-behavioral intervention focusing on psychological aspects of the pain problem.

Publication Type: Review, RCT

PMID: 12071495

Linton SJ. Occupational psychological factors increase the risk for back pain: a systematic review. *J Occup Rehabil*. 2001 Mar;11(1):53-66.

These results suggest that a change in the way we view and deal with back pain is needed. Applying knowledge about psychological factors at work might enhance prevention as well as rehabilitation.

PMID: 11706777

Rating: 1a

Littner M, Hirshkowitz M, Kramer M, Kapen S, Anderson WM, Bailey D, Berry RB, Davila D, Johnson S, Kushida C, Loube DI, Wise M, Woodson BT; American Academy of Sleep Medicine; Standards of Practice Committe. Practice parameters for using polysomnography to evaluate insomnia: an update. *Sleep*. 2003 Sep;26(6):754-60.

PMID: 14572131

Rating: 1b

Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, J Rybak M, Talan DA, Chambers HF; Infectious Diseases Society of America. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis.* 2011 Feb 1;52(3):e18-55.

PMID: 21208910

Rating: 6b

Looper KJ. Potential medical and surgical complications of serotonergic antidepressant medications. Psychosomatics. 2007;48:1-9.

This article reviews the association of serotonergic antidepressants and the following medical complications: syndrome of inappropriate antidiuretic hormone secretion, bleeding, serotonin syndrome, serotonin-discontinuation syndrome, and adverse pregnancy and neonatal effects.

PMID: 17209143

Rating: 5c

Lorberg B, Youssef NA, Bhagwagar Z. Lamotrigine-associated rash: to rechallenge or not to rechallenge? *Int J Neuropsychopharmacol*. 2008 Oct 10:1-9. [Epub ahead of print].

We believe that lamotrigine rechallenge in bipolar depression is an under-utilized option in our clinical armamentarium, and further studies are needed to guide us in this area.

PMID: 18845017

Lundeberg T. Relief of pain from a phantom limb by peripheral stimulation. *J Neurol*. 1985;232(2):79-82.

The results of the present study suggest that vibratory stimulation may be a valuable symptomatic treatment measure in patients suffering pain from a phantom limb.

PMID: 2410571

Rating: 4c

Lynch SS, Cheng CM, Yee JL.Intrathecal ziconotide for refractory chronic pain. *Ann Pharmacother*. 2006;40:1293-300.

Ziconotide is a therapeutic option for treatment of severe chronic pain in patients who have exhausted all other agents, including intrathecal morphine, and for whom the potential benefit outweighs the risks of serious neuropsychiatric adverse effects and of having an implanted device.

PMID: 16849624

Rating: 5a

This article reiterates the warnings on dosage and adverse effects that were outlined by Fisher et al. in 2005.

Lynch ME, Clark AJ, Sawynok J, Sullivan MJ. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. *Anesthesiology*. 2005;103:140-6.

CONCLUSION: This randomized, placebo-controlled trial examining topical 2% amitriptyline, 1% ketamine, and a combination in the treatment of neuropathic pain revealed no difference between groups.

PMID: 15983466

Rating: 2b

Lyseng-Williamson KA, Perry C. Ziconotide. *CNS Drugs*. 2006;20(4):331-8

Ziconotide maintains its analgesic efficacy in preliminary results from long-term, open-label trials (data available for up to 12 months).

PMID: 16599651

Rating: 5b

Mackey SC, Maeda F. Functional imaging and the neural systems of chronic pain. *Neurosurg Clin N Am*. 2004 Jul;15(3):269-88.

Division of Pain Management, Department of Anesthesia, Stanford University Medical Center, Palo Alto, CA 94305, USA. smackey@stanford.edu

Functional neuroimaging is helping to unlock the secrets of the sensory and emotional components of pain and its autonomic responses..

PMID: 15246336

Rating: 5b

Mackie K, Huestis MA, Ratcliffe S, Mead AP. Cannabinoids -- a new class of analgesics. Presentation of the 23rd Annual Meeting of the American Academy of Pain Medicine; February 8, 2007; New Orleans, Louisiana.

Cannabinoids have demonstrated significant analgesic properties, but problems with side effects remain. The CBME compound has been approved in Canada to treat neuropathic pain generated by MS. Obstacles remain to achieving full regulatory and legal approval for cannabis-based medicine in the United States. Eleven states have medical marijuana laws providing patients and caregivers a defense against prosecution; however, federal rulings have created gray areas in how far a practitioner may go to help a patient obtain cannabis.

Rating: 10b

Maclaren JE, Gross RT, Sperry JA, Boggess JT. Impact of opioid use on outcomes of functional restoration. *Clin J Pain*. 2006 May;22(4):392-8.

DISCUSSION: Although further exploration is warranted, results of the current study suggest that opioid use during rehabilitation does not necessarily preclude treatment success.

PMID: 16691094

Rating: 4b

Note: 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

Maier C, Gockel HH, Gruhn K, Krumova EK, Edel MA. Increased risk of suicide under intrathecal ziconotide treatment? - A warning. *Pain.* 2010 Oct 30. [Epub ahead of print]

These cases substantiate the suspicion of a causal relationship between ziconotide and suicidality even in symptom-free patients with a history of depression.

PMID: 21041028

Rating: 5c

Mailis A, Furlan A, Sympathectomy for neuropathic pain (Cochrane Review), Cochrane Database Syst Rev. 2003;(2):CD002918

CONCLUSIONS: 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).

PMID: 12804444

Mailis-Gagnon A, Furlan A, Sandoval J, Taylor R, Spinal cord stimulation for chronic pain, *Cochrane Database Syst Rev*. 2004;3:CD003783

CONCLUSIONS: Although there is limited evidence in favour of SCS for Failed Back Surgery Syndrome and Complex Regional Pain Syndrome Type I, more trials are needed to confirm whether SCS is an effective treatment for certain types of chronic pain.

PMID: 15266501

Rating: 1b

Main CJ, Williams AC, Clinical review ABC of psychological medicine Musculoskeletal pain, *BMJ* 2002;325:534-537 (7 September)

Psychological and social factors have been shown to play a major role in exacerbating the biological substrate of pain by influencing pain perception and the development of chronic disability. This new understanding has led to a "biopsychosocial" model of back pain.

Maizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic non-cancer pain. *Am Fam Physician*. 2005 Feb 1;71(3):483-90.

Tricyclic antidepressants have documented (although limited) efficacy in the treatment of fibromyalgia and chronic low back pain. Recent evidence suggests that duloxetine and pregabalin have modest efficacy in patients with fibromyalgia.

PMID: 15712623

Rating: 5a

Makris UE, Kohler MJ, Fraenkel L. Adverse effects of topical nonsteroidal antiinflammatory drugs in older adults with osteoarthritis: a systematic literature review. *J Rheumatol*. 2010;37:1236-43. Review.

CONCLUSION: Although topical NSAID are safer than oral NSAID (fewer severe gastrointestinal AE), a substantial proportion of older adults report systemic AE with topical agents. The withdrawal rate due to AE with topical agents is comparable to that of oral NSAID.

PMID: 20360183

Rating: 1a

Malanga G, Wolff E. Evidence-informed management of chronic low back pain with nonsteroidal anti-inflammatory drugs, muscle relaxants, and simple analgesics. *Spine J.* 2008;8:173-84.

Articles in this special focus issue were contributed by leading spine practitioners and researchers, who were invited to summarize the best available evidence for a particular intervention and encouraged to make this information accessible to nonexperts

PMID: 18164465

Rating: 5c

Malanga GA, Gwynn MW, Smith R, Miller D. Tizanidine is effective in the treatment of myofascial pain syndrome. *Pain Physician*. 2002; 5:422-32.

Tizanidine was rated as good to excellent in relieving pain by 89% of subjects and 79% of physicians. Tizanidine was effective in the treatment of MPS.

PMID: 16886022

Rating: 4c

Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. *Lancet* 2009;374:1449-61

Two important developments are associated with the decrease in rates of peptic ulcer disease: the discovery of effective and potent acid suppressants, and of Helicobacter pylori.

Nucleoplasty. Evidence is limited showing the effectiveness of percutaneous disc decompression (PDD) with nucleoplasty.

PMID: **1968334**

Rating: 5b
Manchikanti L, Staats PS, Singh V, Schultz DM, Vilims BD, Jasper JF, Kloth DS, Trescot AM, Hansen HC, Falasca TD, Racz GB, Deer TR, Burton AW, Helm S, Lou L, Bakhit CE, Dunbar EE, Atluri SL, Calodney AK, et al. Evidence-based practice guidelines for interventional techniques in the management of chronic spinal pain. *Pain Phys* 2003;6:3-81.

Rating: 6b

Manicourt DH, Brasseur JP, Boutsen Y, Depreseux G, Devogelaer JP. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. *Arthritis Rheum*. 2004 Nov;50(11):3690-7.

CONCLUSION: Our findings support the use of oral alendronate in posttraumatic CRPS I. By reducing local acceleration of bone remodeling, alendronate might relieve pain by effects on nociceptive primary afferents in bone, pain-associated changes in the spinal cord, and possibly also through a central mechanism.

PMID: 15529370

Rating: 2b

Mantyselka PT, Turunen JH, Ahonen RS, Kumpusalo EA. Chronic pain and poor self-rated health*. JAMA*. 2003 Nov 12;290(18):2435-42.

The conclusion was, “Chronic pain is independently related to low self-rated health in the general population.”

PMID: 14612480

Rating: 4a

Marciniak C, Rader L, Gagnon C. The use of botulinum toxin for spasticity after spinal cord injury. *Am J Phys Med Rehabil.* 2008 Apr;87(4):312-7; quiz 318-20, 329.

CONCLUSIONS: BTX seems to be an effective treatment for focal spasticity and for reducing disability in persons with SCI.

PMID: 18356622

Rating: 4b

Maremmani AG, Rovai L, Rugani F, Bacciardi S, Pacini M, Dell'osso L, Maremmani I. Clonazepam as agonist substitution treatment for benzodiazepine dependence: a case report. *Case Rep Psychiatry*. 2013;2013:367594.

PMID: 23424702

Rating: 11a

Marineo G, Iorno V, Gandini C, Moschini V, Smith TJ. Scrambler therapy may relieve chronic neuropathic pain more effectively than guideline-based drug management: results of a pilot, randomized, controlled trial. *J Pain Symptom Manage*. 2012 Jan;43(1):87-95. doi: 10.1016/ j.jpainsymman.2011.03.015.

PMID: 21763099

Rating: 4b

Marinus J, Moseley GL, Birklein F, Baron R, Maihöfner C, Kingery WS, van Hilten JJ.Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol*. 2011 ;10:637-48.

PMID: 21683929

Rating: 5c

Mark TL, Dilonardo J, Vandivort R, Miller K. Psychiatric and medical comorbidities, associated pain, and health care utilization of patients prescribed buprenorphine. *J Subst Abuse Treat.* 2012 Dec 21. doi:pii: S0740-5472(12)00426-6.

PMID: 23265445

Rating: 4b

Maroon JC, Bost JW, Borden MK, Lorenz KM, Ross NA. Natural antiinflammatory agents for pain relief in athletes. *Neurosurg Focus*. 2006 Oct 15;21(4):E11.

The use of both over-the-counter and prescription nonsteroidal medications is frequently recommended, but recent safety concerns must now be considered.. They also review the use of natural supplements, which may be a safer, and often as effective, alternative treatment for pain relief.

PMID: 17112189

Rating: 5a

Lesser-Known Side Effects of NSAIDs - Reduced Healing: Besides the well-documented gastric side effects of NSAIDs and more recently discovered vascular side effects of selective COX-2 inhibitors, there are other less well-known but just as serious effects of NSAIDs, particularly in sports medicine. The use of NSAIDs has been shown to delay and hamper healing in all the soft tissues, including muscles (despite their tremendous blood supply), ligaments, tendons, and cartilage.
Capsaicin (Chili Pepper): 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.

Martin, T., et al. Pharmacology of Opioid and Nonopioid Analgesics in Chronic Pain. The *Journal of Pharmacology and Experimental Therapeutics*. 2001;Volume 299, Number 3: 811-7.

Rating: 1c

Quality: N/A. Total Rating: N/A. Comment: Does not meet inclusion criteria for evidence-based review.

Mason L, Moore RA, Edwards JE, McQuay HJ, Derry S, Wiffen PJ. Systematic review of efficacy of topical rubefacients containing salicylates for the treatment of acute and chronic pain. *BMJ.* 2004 Apr 24;328(7446):995. Epub 2004 Mar 19.

CONCLUSIONS: Based on limited information, topically applied rubefacients containing salicylates may be efficacious in the treatment of acute pain.

PMID: 15033879

Rating: 1c

Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ.* 2004 Apr 24;328(7446):991. Epub 2004 Mar 19.

CONCLUSIONS: Although topically applied capsaicin has moderate to poor efficacy in the treatment of chronic musculoskeletal or neuropathic pain, it may be useful as an adjunct or sole therapy for a small number of patients who are unresponsive to, or intolerant of, other treatments.

PMID: 15033881

Rating: 1c

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. The authors conclude that topical capsaicin is superior to placebo in relieving chronic neuropathic and musculoskeletal pain. Local adverse reactions were common but seldom serious. However, local irritation could have led some patients to recognize active treatment and may have caused biased results. 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.

Mason L, Edwards JE, Moore RA, McQuay HJ. Single dose oral naproxen and naproxen sodium for acute postoperative pain. *The Cochrane Database of Systematic Reviews* 2006 Issue 3

Plain language summary: Naproxen sodium is effective for pain relief in adults who have acute pain after surgery. We found that naproxen sodium taken by mouth at doses of 550 mg and 440 mg is an effective pain killer for treating pain following surgery. The effects of one dose last, on average, up to seven hours.

Rating : 1a

Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for chronic musculoskeletal pain: systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2004;5:28.

CONCLUSIONS: Topical NSAIDs were effective and safe in treating chronic musculoskeletal conditions for two weeks. Larger and longer trials are necessary to fully elucidate the place of topical NSAIDs in clinical practice.

PMID: 15317652

Rating: 1c

Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for acute pain: a meta-analysis. *BMC Fam Pract*. 2004;5:10.

Indirect comparisons of individual topical NSAIDs showed that ketoprofen was significantly better than all other topical NSAIDs, while indomethacin was barely distinguished from placebo.

PMID: 15147585

Rating: 1a

Massey T, Derry S, Moore RA, McQuay HJ. Topical NSAIDs for acute pain in adults. *Cochrane Database Syst Rev.* 2010 Jun 16;6:CD007402.

CONCLUSIONS: Topical NSAIDs can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs, when used to treat acute musculoskeletal conditions.

PMID: 20556778

Rating: 1b

Massó González EL, Patrignani P, Tacconelli S, García Rodríguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis Rheum*. 2010 Jun;62(6):1592-601.

RESULTS: The RR of upper GI bleeding/perforation was 4.50 for traditional NSAIDs and 1.88 for coxibs. Drugs that have a long half-life or slow-release formulation and/or are associated with profound and coincident inhibition of both COX isozymes are associated with a greater risk of upper GI bleeding/perforation.

PMID: 20178131

Rating: 1a

The relative risk of upper gastrointestinal (GI) bleeding varies among the NSAIDs. A table is provided to demonstrate the differences.

Relative Risk of Upper GI Bleeding

NSAID	Relative Risk
Celecoxib	1.42
Ibuprofen	2.23
Diclofenac	3.61
Meloxicam	4.15
Naproxen	4.60
Indomethacin	5.12
Ketoprofen	5.14
Piroxicam	8.00
Ketorolac	14.54

Long-term use of full dosage piroxicam is potentially harmful in older adults due to its long half-life and long duration. Adverse events associated with piroxicam include GI bleeding, renal failure, hypertension, and heart failure. Additionally, as shown in the relative risk table above, piroxicam is second only to ketorolac in its ability to induce gastrointestinal bleeding.

Matthieu L, Meuleman L, Van Hecke E, Blondeel A, Dezfoulian B, Constandt L, Goossens A. Contact and photocontact allergy to ketoprofen. The Belgian experience. *Contact Dermatitis.* 2004;50:238-41.

Dermatologists should be aware of the severity of photoallergic reactions to KP and the risk of cross-sensitization.

PMID: 15186381

Rating: 4b

Matthews P, Derry S, Moore RA, McQuay HJ. Topical rubefacients for acute and chronic pain in adults. *Cochrane Database Syst Rev*. 2009 Jul 8;(3):CD007403.

CONCLUSIONS: The evidence does not support the use of topical rubefacients containing salicylates for acute injuries, and suggests that in chronic conditions their efficacy compares poorly with topical non-steroidal antiinflammatory drugs (NSAIDs). Topical salicylates seem to be relatively well tolerated in the short-term, based on limited data. There is no evidence at all for topical rubefacients with other components.

PMID: 19588430

Rating: 1b

Mayer TG, Gatchel RJ, Kishino N, Keeley J, Capra P, Mayer H, Barnett J, Mooney V. Objective assessment of spine function following industrial injury. A prospective study with comparison group and one-year follow-up. *Spine*. 1985 Jul-Aug;10(6):482-93.

Results demonstrated that the functional capacity measures collected for the treatment group improved in approximately 80% of the patients.

PMID: 2934829

Rating: 3c

Mayer TG, Gatchel RJ, Mayer H, Kishino ND, Keeley J, Mooney V. A prospective two-year study of functional restoration in industrial low back injury. An objective assessment procedure. *JAMA*. 1987 Oct 2;258(13):1763-7.

Analysis demonstrated that 87% of the treatment group was actively working after two years, as compared with only 41% of the nontreatment comparison group.

PMID: 2957520

Rating: 3c

Note: The comparison group consisted of patients denied access to the functional restoration program by their insurers. The two groups were significantly different in terms of medications, with those patients in the treatment arm receiving significantly more opioid medications. The analysis at 2 years was performed only on those patients that the researchers were able to contact.

Mayer T, Polatin P, Smith B, Gatchel R, Fardon D, Herring S, Smith C, Donelson R, Wong D; North American Spine Society Committee; Contemporary Concepts Review Committee. Spine rehabilitation: secondary and tertiary nonoperative care. *Spine J.* 2003 May-Jun;3(3 Suppl):28S-36S.

PMID: 14589215

A review of secondary and tertiary nonoperative care. Includes recommendations for secondary and tertiary treatment.

Rating: 5c

Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. *J Med Toxicol*. 2008;4:2-6.

Renal insufficiency occurs in approximately 1-2% of patients with acetaminophen overdose.

PMID: 18338302

Rating: 5c

McAlindon T, LaValley M, Schneider E, Nuite M, Lee JY, Price LL, Lo G, Dawson-Hughes B. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA*. 2013 Jan 9;309(2):155-62. doi: 10.1001/jama.2012.164487.

PMID: 20091647

Rating: 2a

McBeth J, Pye SR, O'Neill TW, Macfarlane GJ, Tajar A, Bartfai G, Boonen S, Bouillon R, Casanueva F, Finn JD, Forti G, Giwercman A, Han TS, Huhtaniemi IT, Kula K, Lean ME, Pendleton N, Punab M, Silman AJ, Vanderschueren D, Wu FC; EMAS Group. Musculoskeletal pain is associated with very low levels of vitamin D in men: results from the European Male Ageing Study. *Ann Rheum Dis*. 2010 May 24. [Epub ahead of print]

Adjusting for additional lifestyle factors (body mass index, smoking and alcohol use) and depression attenuated these relationships, although pain remained moderately associated with increased odds of 20% of having low vitamin D levels.

PMID: 20498201

Rating: 3a

McBeth J, Lacey RJ, Wilkie R. Predictors of New-Onset Widespread Pain in Older Adults: Results From a Population-Based Prospective Cohort Study in the UK. *Arthritis Rheumatol*. 2014 Mar;66(3):757-67. doi: 10.1002/art.38284.

PMID: 24574238

Rating: 3a

McCarberg BH, Barkin RL. The future of cannabinoids as analgesic agents: a pharmacologic, pharmacokinetic, and pharmacodynamic overview. *Am J Ther.* 2007 Sep-Oct;14(5):475-83.

Therefore, formulation, composition, and delivery system issues will affect the extent to which a particular cannabinoid product may have a desirable risk-benefit profile and acceptable abuse liability potential.

PMID: 17890938

Rating: 5b

McCracken LM, Matthews AK, Tang TS, Cuba SL. A comparison of blacks and whites seeking treatment for chronic pain. *Clinical Journal of Pain*. 2001 Sep;17(3):249-55.

CONCLUSIONS: “These results show that blacks and whites with chronic pain experience pain differently. Several factors may underlie these differences, including family situation, health care experiences, or other unmeasured behavioral, environmental, or social influences.”

Publication Type: Case Control Study, 264 cases

PMID: 11587117

McGettigan P, Henry D. Cardiovascular risk with nonsteroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med* 2011; DOI:10.1371/ Journal.pmed.1001098. Available at: http://www.plosmedicine.org.

This review suggests that among widely used NSAIDs, naproxen and low-dose ibuprofen are least likely to increase cardiovascular risk. Diclofenac in doses available without prescription elevates risk. The data for etoricoxib were sparse, but in pair-wise comparisons this drug had a significantly higher RR than naproxen or ibuprofen. Indomethacin is an older, rather toxic drug, and the evidence on cardiovascular risk casts doubt on its continued clinical use. The updated review includes data from 31 case-control studies with 184,946 cardiovascular events and 21 cohort studies that include outcomes in more than 2.7 million individuals exposed to the drugs.

Rating: 1a

McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: An examination of sales and essential medicine lists in low-, middle-, and high-income countries. *PLoS Med* 2013; DOI:10.1371/journal.pmed.1001388.

Rating: 5b

McDowell BC, Lowe AS, Walsh DM, Baxter DG, Allen JM. The lack of hypoalgesic efficacy of H-wave therapy on experimental ischemic pain. *Pain*. 1995 Apr;61(1):27-32.

These results do not provide convincing evidence for any hypoalgesic effects of H-wave therapy at the frequency parameters stated on the experimental model of pain used.

PMID: 7644244

Rating: 3c..

McDowell BC, McElduff C, Lowe AS, Walsh DM, Baxter GD. The effect of high- and low-frequency H-wave therapy upon skin blood perfusion: evidence of frequency-specific effects. *Clin Physiol.* 1999 Nov;19(6):450-7.

These results provide evidence 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.

PMID: 10583337

Rating: 5c .

Outcome was skin blood flow, not pain relief. No improvement in symptoms or function were examined by this study.

McDowell BC, McCormack K, Walsh DM, Baxter DG, Allen JM. Comparative analgesic effects of H-wave therapy and transcutaneous electrical nerve stimulation on pain threshold in humans. *Arch Phys Med Rehabil.* 1999 Sep;80(9):1001-4.

CONCLUSION:
H-wave therapy and TENS both provided localized hypoalgesia during stimulation and for up to 5 minutes after it. No frequency- or modality-specific effects between the groups.

PMID: 10488999

Rating: 2c.

A total of 48 subjects were divided into 6 groups, leaving each group presumably with 8 members, and it is not clear that these results would be statistically significant in any case; but the study showed no difference between the effects of TENS and H-wave.

McGeary DD, Mayer TG, Gatchel RJ. High pain ratings predict treatment failure in chronic occupational musculoskeletal disorders. *J Bone Joint Surg Am*. 2006 Feb;88(2):317-25.

They were also twice as likely to claim a new injury to the same musculoskeletal site after returning to work and to fail to settle Workers' Compensation or third-party financial disputes.

PMID: 16452743

Rating: 3c

McGeary DD, Mayer TG, Gatchel RJ, Anagnostis C. Smoking status and psychosocioeconomic outcomes of functional restoration in patients with chronic spinal disability. *Spine J*. 2004 Mar-Apr;4(2):170-5.

CONCLUSIONS: Contrary to popular belief, CDWRSD patients who smoke do not differ significantly in socioeconomic or psychosocial outcomes relative to those who do not. Although this study does indicate that those who smoke more evidence lower rehabilitation completion rates, those who completed the program had identical 1-year posttreatment outcomes of socioeconomic importance except in retraining work at year end as those who did not smoke. Smokers had slightly higher posttreatment self-reported pain and disability ratings mixed and limited. Overall, there is evidence for the widely held belief that smoking negatively affects tertiary rehabilitation.

PMID: 15016394

Rating: 3c

McLean W, Boucher E, Brennan M. et al. Is there An Indication for the Use of Barbituate-Containing Analgesic Agents in the Treatment of Pain. Guidelines for Their Safe Use and Withdrawl Management. *Canadian Journal of Clin Pharm* 2000;(7)4:191-197. (February 20, 2001).

Extrapolation from published reports on abuse and withdrawal syndrome with these drugs suggests that BCAs have the potential to produce drug dependence and addictive behaviour, especially with regular use.

Publication Type: Guideline, Practice Guideline

PMID: 11118965

McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain.* 1996 Dec;68(2-3):217-27.

With very similar results for anticonvulsants it is still unclear which drug class should be first choice.

PMID: 9121808

Rating: 1b

Medtronic, MDT Webpage, Indications for stimulator (medtronic) implantation, 2008

Rating: 5c

Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaw. *Hematology Am Soc Hematol Educ Program*. 2006:356-60, 515.

Post-marketing experience with this class of agents, particularly the more potent intravenous agents pamidronate and zoledronic acid, have raised cautionary notes regarding the potential side effects.

PMID: 17124083

Rating: 5b

Meier MH, Murray RM. Cannabis Use in Teens Linked to Irreparable Drop in IQ. 14th International Congress on Schizophrenia Research (ICOSR). Abstract S267. Presented April 25, 2013.

Rating: 10a

Melhorn JM. Workers' compensation: avoiding work-related disability. *J Bone Joint Surg Am.* 2000 Oct;82-A(10):1490-3.

The Hand Center, Wichita, Kansas 67208-4510, USA.

PMID: 11057476

Mellin G, Härkäpää K, Hurri H, Järvikoski A. A controlled study on the outcome of inpatient and outpatient treatment of low back pain. Part IV. Long-term effects on physical measurements. *Scand J Rehabil Med*. 1990;22:189-94.

Statistically significant but modest correlations were found between improved physical functions and subjective progress during the long-term follow-ups.

PMID: 2148222

Rating: 2c

Menigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. *Anesth Analg*. 2005 May;100(5):1394-9, table of contents.

In conclusion, premedication with 1200 mg gabapentin improved preoperative anxiolysis, postoperative analgesia, and early knee mobilization after arthroscopic anterior cruciate ligament repair.

PMID: 15845693

Rating: 2b

Mueller SR, Walley AY, Calcaterra SL, Glanz JM, Binswanger IA. A Review of Opioid Overdose Prevention and Naloxone Prescribing: Implications for Translating Community Programming into Clinical Practice. Subst Abus. 2015:0.

PMID: 25774771

Rating: 5c

Miller L, Mattison P, Paul L, Wood L. The effects of transcutaneous electrical nerve stimulation (TENS) on spasticity in multiple sclerosis. *Mult Scler.* 2007 May;13(4):527-33. Epub 2007 Jan 29.

Thus, this study suggests that, whilst TENS does not appear to be effective in reducing spasticity, longer applications may be useful in treating MS patients with pain and muscle spasm.

PMID: 17463075

Rating: 2b

Miner PB Jr, McKean LA, Gibb RD, Erasala GN, Ramsey DL, McRorie JW. Omeprazole-Mg 20.6 mg is superior to lansoprazole 15 mg for control of gastric acid: a comparison of over-the-counter doses of proton pump inhibitors. *Aliment Pharmacol Ther.* 2010 Apr;31(8):846-51. Epub 2010 Feb 8.

CONCLUSION: Omeprazole-Mg 20.6 mg provided a statistically significantly ($P < 0.0001$) greater acid control than lansoprazole 15 mg.

PMID: 20146702

Rating: 2b

Mitchinson AR, Kim HM, Rosenberg JM, Geisser M, Kirsh M, Cikrit D, Hinshaw DB. Acute postoperative pain management using massage as an adjuvant therapy: a randomized trial. *Arch Surg.* 2007 Dec;142(12):1158-67.

CONCLUSION: Massage is an effective and safe adjuvant therapy for the relief of acute postoperative pain in patients undergoing major operations.

PMID: 18086982

Rating: 2b

"Massage is an effective and safe adjuvant therapy for the relief of acute postoperative pain in patients undergoing major operations," the authors write. "With proper training, health care providers at the bedside (especially nurses) may now have a powerful nonpharmacologic tool to directly address their patients' pain and anxiety." Massage therapy in postoperative patients results in faster rate of decrease in pain intensity and pain unpleasantness, but not anxiety, in the first 4 postoperative days.

Mitte K. A meta-analysis of the efficacy of psycho- and pharmacotherapy in panic disorder with and without agoraphobia. *J Affect Disord*. 2005; 88:27-45.

After a comprehensive review of the literature, the results of 124 studies were included. (C)BT was more effective than a no-treatment control and a placebo control. Pharmacotherapy was more effective than a placebo control; there was no superiority of any drug class. (C)BT was at least as effective as pharmacotherapy and depending on type of analysis even significantly more effective.

PMID: 16005982

Rating: 1b

Montgomery B. Does paracetamol cause hypertension? *BMJ*. 2008;336:1190-1.

Rating: 5c

Moon JY, Park SY, Kim YC, Lee SC, Nahm FS, Kim JH, Kim H, Oh SW. Analysis of patterns of three-phase bone scintigraphy for patients with complex regional pain syndrome diagnosed using the proposed research criteria (the 'Budapest Criteria'). *Br J Anaesth*. 2012;108:655-61.

PMID: 22293544

Rating: 3b

Moore A, Wiffen P, Kalso E. Antiepileptic drugs for neuropathic pain and fibromyalgia. *JAMA*. 2014 Jul;312(2):182-3. doi: 10.1001/jama.2014.6336.

PMID: 25005656

Rating: 1b

Moore, S and Shurman J. Combined Neuromuscular Electrical Stimulation and Transcutaneous Electrical Nerve Stimulation for Treatment of Chronic Back Pain: A Double-Blind, Repeated Measures Comparison. *Archive of Physical Medicine and Rehabilitation*. 1997; Volume 78, January: 55-60.

Rating: 2c

Quality: Low. Total Rating: 3.5. Comment: Does not meet inclusion criteria for evidence-based review.

Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev*. 2009 Jul 8;(3):CD007076.

CONCLUSIONS: Pregabalin has proven efficacy in neuropathic pain conditions and fibromyalgia.

PMID: 19588419

Rating: 1a

Moore TM, Jones T, Browder JH, Daffron S, Passik SD. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. *Pain Med.* 2009;10:1426-33.

Among patients who were discontinued from opioids for aberrant drug-related behaviors, the clinical interview and the SOAPP were most effective at predicting risk at baseline.

PMID: 20021601

Rating: 3c

Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther*. 2005;7:R1046-51.

PMID: 16207320

Rating: 1c

Morgan CJ, Curran HV; Independent Scientific Committee on Drugs. Ketamine use: a review. *Addiction*. 2012;107:27-38.

A major physical harm is ketamine induced ulcerative cystitis which, although its aetiology is unclear, seems particularly associated with chronic, frequent use of the drug. Frequent, daily use is also associated with neurocognitive impairment and, most robustly, deficits in working and episodic memory. Recent studies suggest certain neurological abnormalities which may underpin these cognitive effects. Many frequent users are concerned about addiction and report trying but failing to stop using ketamine.

PMID: 21777321

Rating: 5b

Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia*. Pharmacotherapy.* 2007 Jan;27(1):89-110.

Insomnia, defined as difficulty falling asleep, staying asleep, and/or experiencing restorative sleep with associated impairment or significant distress, is a common condition resulting in significant clinical and economic consequences. Nonpharmacologic options include stimulus control, sleep hygiene education, sleep restriction, paradoxical intention, relaxation therapy, biofeedback, and cognitive behavioral therapy.

Rating: 1b

Morin CM, Vallières A, Guay B, Ivers H, Savard J, Mérette C, Bastien C, Baillargeon L. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. *JAMA*. 2009 May 20;301(19):2005-15.

CONCLUSION: In patients with persistent insomnia, the addition of medication to CBT produced added benefits during acute therapy, but long-term outcome was optimized when medication is discontinued during maintenance CBT.

PMID: 19454639

Rating: 2a

Morin CM, Bastien C, Guay B, Radouco-Thomas M, Leblanc J, Vallières A. Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia*. Am J Psychiatry*. 2004;161:332-42.

The addition of cognitive behavior therapy alleviates insomnia, but sleep improvements may become noticeable only after several months of benzodiazepine abstinence.

PMID: 14754783

Rating: 2b

Mork PJ, Vasseljen O, Nilsen TI. Association between physical exercise, body mass index, and risk of fibromyalgia: longitudinal data from the Norwegian Nord-Trøndelag Health Study. *Arthritis Care Res (Hoboken)*. 2010 May;62(5):611-7.

CONCLUSION: Being overweight or obese was associated with an increased risk of FM, especially among women who also reported low levels of physical exercise.

PMID: 20191480

Rating: 3a

Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain*. 1999 Mar;80(1-2):1-13.

We conclude that active psychological treatments based on the principle of cognitive behavioural therapy are effective.

PMID: 10204712

Rating: 1a

Moskowitz M, Mackie K, Huestis MA, Ratcliffe S, Mead AP, Fishman SM. Cannabinoids - a new class of analgesics. Program and abstracts of the American Academy of Pain Medicine 23rd Annual Meeting; February 7-10, 2007; New Orleans, Louisiana.

In total, 11 states have approved the use of medical marijuana for the treatment of chronic pain or for nausea associated with chemotherapy. The medical community has lagged behind a bit and partly because there are really very little, 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. It is difficult to justify advising our patients to smoke street-grade marijuana, presuming that they will experience benefit, when they may also be harmed.

Rating: 10a

Moulin DE, Systemic drug treatment for chronic musculoskeletal pain, *Clin J Pain*. 2001 Dec;17(4 Suppl):S86-93.

CONCLUSIONS: For chronic pain, opioid analgesics provide benefit for up to 9 weeks (level 2). For chronic low back pain, the evidence shows that various types of nonsteroidal antiinflammatory drugs are equally effective or ineffective, and that antidepressants provide no benefit in the short to intermediate term (level 2).

PMID: 11783837

Rating: 5b

Murray AK, Herrick AL, King TA. Laser Doppler imaging: a developing technique for application in the rheumatic diseases. *Rheumatology (Oxford)*. 2004;43:1210-8.

PMID: 15226515

Rating: 5c

Nakazawa, R., et al. Hormone Profiles after Intramuscular Injection of Testosterone Enanthate in Patients with Hypogonadism. *Endocrine Journal*, 2006; Volume 53, Number 3, 305-103.

Rating: 2c

Quality: Low. Total Rating: .5. Comment: Does not meet inclusion criteria for evidence-based review.

Naliboff BD, Wu SM, Pham Q. Clinical considerations in the treatment of chronic pain with opiates*. J Clin Psychol*. 2006;62:1397-408. 2006 Aug 25; [Epub ahead of print]

Practice guidance is offered regarding long-term opiate treatment, including definitions of addiction, initial assessments, ongoing substance misuse monitoring, use of psychological assessment instruments, and managing medication misuse problems.

PMID: 16937352

Rating: 5a

Namaka M, Gramlich CR, Ruhlen D, Melanson M, Sutton I, Major J. A treatment algorithm for neuropathic pain. *Clin Ther*. 2004 Jul;26(7):951-79.

RESULTS: Any of the agents in the first-line drug classes (tricyclic antidepressants, antiepileptic drugs, topical antineuralgics, analgesics) may be used as a starting point in the treatment of neuropathic pain. If a patient does not respond to treatment with at least 3 different agents within a drug class, agents from a second drug class may be tried.

PMID: 15336464

Rating: 8a

Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, Jamison RN. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain*. 2008 Mar;9(3):254-64. Epub 2007 Dec 21.

The results of our preliminary study suggest that dronabinol, a synthetic THC, may have an additive effect on pain relief.

PMID: 18088560

Rating: 2b

Naumann M, So Y, Argoff CE, Childers MK, Dykstra DD, Gronseth GS, Jabbari B, Kaufmann HC, Schurch B, Silberstein SD, Simpson DM; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment:Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008 May 6;70(19):1707-14.

Botulinum neurotoxin (BoNT) may be considered for gustatory sweating and low back pain (Level C). BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B).

PMID: 18458231

Rating: 1c

Nelemans PJ, Bie RA de, Vet HCW de, Sturmans F. Injection therapy for subacute and chronic benign low back pain (Cochrane Review). In: *The Cochrane Library,* Issue 2, 2002. Oxford: Update

Convincing evidence is lacking on the effects of injection therapies for low back pain.

Rating: 1b

Nelson DV. Pieces of the puzzle: management of complex regional pain syndrome. *Clin J Pain*. 2006; 22:413-4.

The authors for this special series have generally been in the forefront of their respective disciplines in refining the focus on important issues about CRPS or neuropathic pain more broadly. Functional restoration was stressed.

Rating: 5b

Nelson LS, Perrone J. Curbing the opioid epidemic in the United States: the risk evaluation and mitigation strategy (REMS). *JAMA*. 2012 Aug 1;308(5):457-8.

PMID: 22851109

Rating: 5b

Neogi T, Felson DT, Sarno R, Booth SL. Vitamin K in hand osteoarthritis: results from a randomised clinical trial. *Ann Rheum Dis.* 2008 Nov;67(11):1570-3. Epub 2008 Jul 14.

CONCLUSIONS: There was no overall effect of vitamin K on radiographic hand osteoarthritis.

PMID: 18625626

Rating: 2b

Neogi T, Booth SL, Zhang YQ, Jacques PF, Terkeltaub R, Aliabadi P, Felson DT. Low vitamin K status is associated with osteoarthritis in the hand and knee. *Arthritis Rheum*. 2006 Apr;54(4):1255-61.

CONCLUSION: These observational data support the hypothesis of an association between low plasma levels of vitamin K and increased prevalence of OA manifestations in the hand and knee.

PMID: 16572460

Rating: 3a

Newton-John TR, Spence SH, Schotte D. Cognitive-behavioural therapy versus EMG biofeedback in the treatment of chronic low back pain. *Behav Res Ther*. 1995 Jul;33(6):691-7.

Results at post-treatment indicated significant improvements in functioning on measures of pain intensity, perceived level of disability, adaptive beliefs about pain and the level of depression in both the CBT and EMGBF conditions. No significant differences were found between CBT and EMGBF on any of the outcome measures at either post-treatment or at 6 months follow-up.

PMID: 7654161

Rating: 2c

Ney JP, Difazio M, Sichani A, Monacci W, Foster L, Jabbari B. Treatment of chronic low back pain with successive injections of botulinum toxin a over 6 months: a prospective trial of 60 patients. *Clin J Pain.* 2006 May;22(4):363-9.

CONCLUSIONS: Botulinum toxin A improves refractory chronic low back pain with a low incidence of side effects. The beneficial clinical response is sustained with a second treatment.

PMID: 16691090

Rating: 4c

NICE (National Institute for Health and Clinical Excellence). Pain (chronic neuropathic or ischaemic) - spinal cord stimulation: final appraisal determination. 01 September 2008.

1 Guidance: 1.1 Spinal cord stimulation is recommended as a treatment option for adults with chronic pain of neuropathic origin who: • continue to experience chronic pain (measuring at least 50 mm on a 0–100 mm visual analogue scale) for at least 6 months despite appropriate conventional medical management, and • who have had a successful trial of stimulation as part of the assessment specified in recommendation 1.3. Neuropathic conditions include failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS).

Rating: 8a

Nielsen OH, Ainsworth M, Csillag C, Rask-Madsen J. Systematic review: coxibs, non-steroidal anti-inflammatory drugs or no cyclooxygenase inhibitors in gastroenterological high-risk patients? *Aliment Pharmacol Ther*. 2006 Jan 1;23(1):27-33.

Clinicians should, therefore, never prescribe coxibs to patients with cardiovascular risk factors, and should only reluctantly prescribe coxibs to patients with a history of ulcer disease or dyspepsia to overcome persistent pain due to, e.g. rheumatoid arthritis or osteoarthritis. Instead, they should consider using conventional non-steroidal anti-inflammatory drugs in combination with a proton pump inhibitor or a prostaglandin analogue, especially for patients with increased cardiovascular risks.

PMID: 16393277

Rating: 5a

Niethard FU, Gold MS, Solomon GS, Liu JM, Unkauf M, Albrecht HH, Elkik F. Efficacy of topical diclofenac diethylamine gel in osteoarthritis of the knee. *J Rheumatol*. 2005;32:2384-92.

CONCLUSION: Diclofenac gel was effective and safe for relief of symptoms of OA of the knee over 3 weeks of dosing.

PMID: 16331769

Rating: 1c

Nifosì F, Violato E, Pavan C, Sifari L, Novello G, Guarda Nardini L, Manfredini D, Semenzin M, Pavan L, Marini M. Psychopathology and clinical features in an Italian sample of patients with myofascial and temporomandibular joint pain: preliminary data. *Int J Psychiatry Med*. 2007;37:283-300.

Psychiatric evaluation: Myofascial pain patients had higher scores for personal psychiatric history and a history of more frequent psychotropic drug use. --HDRS and HARS: The sample presented scores indicating mild depressive symptoms and moderate anxiety symptoms.

PMID: 18314857

Rating: 4b

Niv D, Maltsman-Tseikhin A. Postherpetic neuralgia: the never-ending challenge. *Pain Pract*. 2005 Dec;5(4):327-40.

Interventions with low risk, such as transcutaneous electrical nerve stimulation (TENS), are appropriate.

PMID: 17177766

Rating: 5b

Noize P, Bénard-Laribière A, Aulois-Griot M, Moore N, Miremont-Salamé G, Haramburu F. Cutaneous adverse effects of ketoprofen for topical use: clinical patterns and costs. *Am J Clin Dermatol.* 2010;11:131-6.

Since its introduction in France, ketoprofen for topical use has been associated with a large number of cutaneous adverse effect reports. Generalized lesions were observed in 37.5% of patients.

PMID: 20141234

Rating: 4a

Noppers IM, Niesters M, Aarts LP, Bauer MC, Drewes AM, Dahan A, Sarton EY. Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. *Pain.* 2011 Sep;152(9):2173-8.

Our data suggest an increased risk for development of ketamine-induced liver injury when the infusion is prolonged and/or repeated within a short time frame.

PMID: 21546160

Rating: 4c

Nouwen A. EMG biofeedback used to reduce standing levels of paraspinal muscle tension in chronic low back pain. *Pain*. 1983 Dec;17(4):353-60.

Compared to patients in the waiting list control group, those who received EMG biofeedback showed a significant decrease in standing paraspinal EMG from pretreatment to post-treatment baseline. However, no significant differences in reported pain were found during these periods. It is concluded that reduction of standing paraspinal EMG does not lead to reduction in pain.

PMID: 6229707

Rating: 2c

Orthopaedic Section BOD. *Guideline: Occupational Health Physical Therapy: Advanced Work Rehabilitation Guidelines.* Approved July 11, 2011. (Formerly the APTA guideline, rescinded in May 2011)

"The purpose of this document is to establish guidelines for the practice of Work Rehabilitation in a manner that promotes clinical excellence, accountability and consistency through evidence based services. These guidelines are to be used in context with the APTA *Standards of Practice for Physical Therapy* and the Accompanying Criteria, the APTA *Guide to Physical Therapist Practice, Second Edition,* and the standard language and framework for health and health-related states that is described in the World Health Organization (WHO)*International Classification of Functioning, Disability and Health,* known more commonly as ICF."

Rating:

Novak S, Nemeth WC, Lawson KA. Trends in medical use and abuse of sustained-release opioid analgesics: a revisit. *Pain Med*. 2004 Mar;5(1):59-65.

CONCLUSION: Using this method of analysis, the rates of drug abuse, and resultant morbidity secondary to the use of opioid analgesics, remain low in spite of the increase in medical use of these substances.

PMID: 14996238

Rating: 4a

Novak S, Nemeth WC. How clinically relevant is a meta-analysis of electrical nerve stimulation when based on heterogeneous disease states? *Pain.* 2007 Sep;131(1-2):228-9; author reply 229-30. Epub 2007 Jul 26.

Comment on: Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: A meta-analysis of randomized controlled trials. Pain. 2007 Jul;130(1-2):157-65.

PMID: 17662532

Rating: 11b

It is unclear as to how helpful this study is for recommendations for clinical treatment. Musculoskeletal pain does have multiple pathophysiological mechanisms (nociceptive, neuropathic, central, etc.) which would appear to prohibit a generalization that is useful for a meta-analysis of this type. The grouping of inflammatory disease states into the study population mix is particularly troublesome due to the acute nociceptive pain features concomitant in this chronic disease state. It would therefore appear that due to the tremendous heterogeneity of the analyzed studies that a statement as strong as “ENS is an effective treatment modality for chronic musculoskeletal pain” overextends the final interpretation of this statistical analysis.

Oaklander AL, Fields HL. Is reflex sympathetic dystrophy/complex regional pain syndrome type I a small-fiber neuropathy? *Ann Neurol*. 2009;65:629-38.

PMID: 19557864

Rating: 5c

Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). *Pain.* 2006 ;120:235-43.

PMID: 16427737

Rating: 4c

Oaklander AL, Herzog ZD, Downs H, Klein MM. Objective evidence that small-fiber polyneuropathy underlies some illnesses currently labeled as fibromyalgia. *Pain.* 2013. doi:pii: S0304-3959(13)00294-7. 10.1016/j.pain.2013.06.001.

PMID: 23748113

Rating: 4c

O'brien CP. Benzodiazepine use, abuse, and dependence. *J Clin Psychiatry*. 2005;66 :28-33

It is important to distinguish between addiction to and normal physical dependence on benzodiazepines. Intentional abusers of benzodiazepines usually have other substance abuse problems.

PMID: 15762817

Rating: 5b

Ochoa JL, Verdugo RJ. Neuropathic pain syndrome displayed by malingerers. *J Neuropsychiatry Clin Neurosci*. 2010;22:278-86.

PMID: 20686134

Rating: 3c

O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database Syst Rev*. 2013; 4:CD009416. doi: 10.1002/14651858.CD009416.pub2.

PMID: 23633371

Rating: 1b

O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med*. 2009;122:S22-32.

On the basis of randomized clinical trials, medications recommended as first-line treatments for neuropathic pain included certain antidepressants (i.e., tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel alpha(2)-delta ligands (i.e., gabapentin and pregabalin), and topical lidocaine.

PMID: 19801049

Rating: 5b

Ojala T, Arokoski JP, Partanen J. The effect of small doses of botulinum toxin a on neck-shoulder myofascial pain syndrome: a double-blind, randomized, and controlled crossover trial. *Clin J Pain*. 2006 Jan;22(1):90-6.

Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland. tuula.ojala@kuh.fi

OBJECTIVES: Myofascial pain syndrome is a common cause of muscular pain in the shoulder-neck region. Injections of large amounts of botulinum toxin A have been found to be beneficial for the alleviation of myofascial pain, but large doses of this toxin may cause paresis of the muscle and other adverse events. CONCLUSIONS: Our study shows that there was no difference between the effect of small doses of botulinum toxin A and those of physiological saline in the treatment of myofascial pain syndrome.

PMID: 16340597

Rating: 2c

Oka H, Akune T, Muraki S, En-yo Y, Yoshida M, Saika A, Sasaki S, Nakamura K, Kawaguchi H, Yoshimura N. Association of low dietary vitamin K intake with radiographic knee osteoarthritis in the Japanese elderly population: dietary survey in a population-based cohort of the ROAD study. *J Orthop Sci.* 2009 Nov;14(6):687-92. Epub 2009 Dec 8.

CONCLUSIONS: The present cross-sectional study using a population-based cohort supports the hypothesis that low dietary vitamin K intake is a risk factor for knee OA. Vitamin K may have a protective role against knee OA and might lead to a disease-modifying treatment.

PMID: 19997813

Rating: 3a

Okun MS, Nadeau SE, Rossi F, Triggs WJ. Immobilization dystonia*. J Neurol Sci*. 2002 15;201:79-83.

PMID: 12163198

Rating: 4c

O'Lenic K. Vimpat for neuropathic pain. April 09, 2012.

Rating: 10a

Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, Göbel H, Lainez MJ, Lance JW, Lipton RB, Nappi G, Sakai F, Schoenen J, Silberstein SD, Steiner TJ, Headache Classification Committee. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia*. 2006; 26:742-6.

The system of being able to use CM and the medication overuse headache (MOH) diagnosis only after discontinuation of overuse has proven highly unpractical and new data have suggested a much more liberal use of these diagnoses. It is now recommended that the MOH diagnosis should no longer request improvement after discontinuation of medication overuse but should be given to patients if they have a primary headache plus ongoing medication overuse.

PMID: 16686915

Rating: 5b

Oluwajenyo Banjo MPHc, Tzemis D, Al-Qutub D, Amlani A, Kesselring S, Buxton JA. A quantitative and qualitative evaluation of the British Columbia Take Home Naloxone program. CMAJ Open. 2014; 2:E153-61.

PMID: 25295235

Rating: 11b

Osenbach RK, Harvey S. Neuraxial infusion in patients with chronic intractable cancer and noncancer pain. *Curr Pain Headache Rep*. 2001 Jun;5(3):241-9.

Initially, spinal infusion therapy was indicated only for patients with cancer pain that could not be adequately controlled with systemic narcotics. Consequently, long-term efficacy has not been as significant as had been hoped.

PMID: 11309212

Rating: 5b

Ostelo RW, van Tulder MW, Vlaeyen JW, Linton SJ, Morley SJ, Assendelft WJ. Behavioural treatment for chronic low-back pain. *Cochrane Database Syst Rev*. 2005 Jan 25;(1):CD002014.

No significant differences could be detected between behavioural treatment and exercise therapy. Whether clinicians should refer patients with CLBP to behavioural treatment programs or to active conservative treatment cannot be concluded from this review.

PMID: 15674889

Rating: 1a

Otis JD, Macdonald A, Dobscha SK. Integration and coordination of pain management in primary care. *J Clin Psychol*. 2006 Aug 25; [Epub ahead of print]

We address the integration and coordination of care between mental health and primary care.

PMID: 16937344

Rating: 5b

Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *Am J Psychiatry*. 2001;158:1989-92.

CONCLUSIONS: Early studies of small samples may have led to initial overestimations of the efficacy of SSRIs for panic disorder.

PMID: 11729014

Rating: 1b

Owens C, Pugmire B, Salness T, Culbertson V, Force R, Cady P, Steiner J. Abuse potential of carisoprodol: a retrospective review of Idaho Medicaid pharmacy and medical claims data. *Clin Ther*. 2007;29:2222-5.

PMID: 18042478

Rating: 3b

Page, S., et al. Exogenous Testosterone (T) alone or with Finasteride Increases Physical Performance, Grip Strength, and Lean Body Mass in Older Men with Low Serum T. *Journal of Clinical Endocrinology & Metabolism*, Volume 90, Number 3, 1502-1510. 2005.

Rating: 2b

Quality: Intermediate. Total Rating: 7.0. Comment: Study looks at an older population of men than typically represented in the Work Comp setting 70+. Has a high dropout rate. However, it does score high in areas of randomization and blinding. In the end it finds that Exogenous Testosterone therapy and Exogenous Testosterone therapy with Finasteride Increases Physical Performance and can increase physical function in older men with low levels of serum Testosterone.

Paice JA, Winkelmuller W, Burchiel K, Racz GB, Prager JP. Clinical realities and economic considerations: efficacy of intrathecal pain therapy. *J Pain Symptom Manage.* 1997 Sep;14(3 Suppl):S14-26.

In both studies, patients reported significant improvement in activities of daily living, quality of life measures, and satisfaction with the therapy.

PMID: 9291707

Rating: 1b

Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB, Singh U, Singh PK. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study. J Neurosurg Anesthesiol. 2005 Apr;17(2):65-8.

Thus, gabapentin 600 mg is the optimal dose for postoperative pain relief following lumbar diskectomy.

PMID: 15840990

Rating: 2b

Pang D, Jones GT, Power C, Macfarlane GJ. Influence of childhood behaviour on the reporting of chronic widespread pain in adulthood: results from the 1958 British Birth Cohort Study. Rheumatology (Oxford). 2010 Mar 9. [Epub ahead of print]

Conclusion. Maladjusted (social) behaviour is associated with increased long-term CWP beyond childhood and adolescence.

PMID: 20215340

Rating: 3a

Pankaj A, Kotwal PP, Mittal R, Deepak KK, Bal CS. Diagnosis of post-traumatic complex regional pain syndrome of the hand: current role of sympathetic skin response and three-phase bone scintigraphy. *J Orthop Surg (Hong Kong).* 2006;14:284-90.

PMID: 17200530

Rating: 4c

Parr JM, Kavanagh DJ, Cahill L, Mitchell G, McD Young R. Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. *Addiction*. 2009;104:13-24.

PMID: 18983627

Rating: 1b

Efficacy of Outpatient Ketamine Infusions in Refractory Chronic Pain Syndromes: A 5-Year Retrospective Analysis. *Pain Med.* 2011 Sep 21. doi: 10.1111/j.1526-4637.2011.01241.x.

Results. We identified 49 patients. Conclusions. We conclude that in patients with severe refractory pain of multiple etiologies, subanesthetic ketamine infusions may improve VAS scores..

PMID: 21939497

Rating: 4c

Patrick LE, Altmaier EM, Found EM. Long-term outcomes in multidisciplinary treatment of chronic low back pain: results of a 13-year follow-up. *Spine.* 2004 Apr 15;29(8):850-5.

CONCLUSIONS: The data lend support to the long-term effectiveness of multidisciplinary treatment programs for chronic low back pain.

PMID: 15082983

Rating: 4c

Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC, Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study, *Arch Intern Med*. 2002 Oct 14;162(18):2113-23.

PMID: 12374520

Rating: 2b

P-Codrea Tigaran S, Sidenius P, Dam M. Lamotrigine-induced rash--worth a rechallenge. *Acta Neurol Scand.* 2005 Mar;111(3):191-4.

CONCLUSION: This study is the first one to provide a successful recipe verified in time for the rechallenge with LTG after the initial drug-induced rash.

PMID: 15736314

Rating: 4b

Peloso PM, Gross AR, Haines TA, Trinh K, Goldsmith CH, Aker P. Medicinal and injection therapies for mechanical neck disorders: a cochrane systematic review. *J Rheumatol*. 2006 May;33(5):957-67.

CONCLUSION: Intramuscular injection of lidocaine for chronic MND and intravenous injection of methylprednisolone for acute whiplash were effective treatments. There was limited evidence of effectiveness of epidural injection of methylprednisolone and lidocaine for chronic MND with radicular findings. Muscle relaxants and nonsteroidal antiinflammatory drugs have unclear benefits. There was moderate evidence that Botox-A intramuscular injections for chronic MND were not better than saline.

PMID: 16652427

Rating: 1b

Peng PW, Wijeysundera DN, Li CC. Use of gabapentin for perioperative pain control -- a meta-analysis. *Pain Res Manag*. 2007 Summer;12(2):85-92.

CONCLUSION: Gabapentin improves the analgesic efficacy of opioids both at rest and with movement, reduces analgesic consumption and opioid-related adverse effects, but is associated with an increased incidence of sedation and dizziness.

PMID: 17505569

Rating: 1c

Peng P, Tumber P, Stafford M, Gourlay D, Wong P, Galonski M, Evans D, Gordon A. Experience of methadone therapy in 100 consecutive chronic pain patients in a multidisciplinary pain center. *Pain Med*. 2008;9:786-94

CONCLUSION: From our experience, methadone is an effective alternative to conventional opioids for chronic pain management when used by experienced clinicians in a setting that allows for close monitoring and careful dose initiation and adjustment.

PMID: 18564997

Rating: 4b

This is a well-done review of the use of methadone in a pain practice, including advice on monitoring and dose conversion.

Perez R, Kwakkel G, Zuurmond W, et al. Treatment of Reflex Sympathetic Dystrophy (CRPS Type 1): A Research Synthesis of 21 Randomized Clinical Trials. *J Pain Symptom Manage* 2001:21:511-526.

Except for the calcitonin subgroup (P = 0.002), the quality-weighted summary effect size of these subgroups were not significant. No significant analgesic effect by sympathetic suppressing agents could be established. Calcitonin seems to provide effective pain relief in reflex sympathetic dystrophy patients.

Publication Type: Meta-Analysis

PMID: 11397610

Perez RS, Keijzer C, Bezemer PD, Zuurmond WW, de Lange JJ. Predictive value of symptom level measurements for complex regional pain syndrome type I. Eur J Pain. 2005 Feb;9(1):49-56.

We conclude that the measured pain, temperature, volume and range of motion can be used as diagnostic indicators for establishing presence or absence of CRPS I.

Rating: 4b

Perez RS, Zollinger PE, Dijkstra PU, Thomassen-Hilgersom IL, Zuurmond WW, Rosenbrand KC, Geertzen JH; CRPS I task force. Evidence based guidelines for complex regional pain syndrome type 1. *BMC Neurol*. 2010;10:20. doi: 10.1186/1471-2377-10-20.

PMID: 20356382

Rating: 1c

We identified 77 studies and 12 meta-analyses and literature review on the use of antidepressant to treat painful rheumatological conditions. Forty-nine of these clinical studies

Perrot S, Maheu E, Javier RM, Eschalier A, Coutaux A, LeBars M, Bertin P, Bannwarth B, Treves R. Guidelines for the use of antidepressants in painful rheumatic conditions. *Eur J Pain.* 2006 Apr;10(3):185-92. Epub 2005 Apr 18.
were considered valid and were used to develop the recommendations.

PMID: 16490727

Rating: 8a

Perrot S, Javier RM, Marty M, Le Jeunne C, Laroche F. Antidepressant use in painful rheumatic conditions. *Rheum Dis Clin North Am*. 2008;34:433-53.

Clinical studies have shown that tricyclic antidepressants, even at low doses, have analgesic effects in rheumatologic conditions equivalent to those of serotonin and noradrenalin reuptake inhibitors, but are less well tolerated.

PMID: 18638685

Rating: 5a

Peterson K, McDonagh M, Thakurta S, Dana T, Roberts C, Chou R, Helfand M. Drug class review: Nonsteroidal antiinflammatory drugs (NSAIDs). Update 4 final report. Accessed 10/2011.

The purpose of this study to compare effectiveness and harms of oral or topical NSAIDs. For pain relief, there were no significant differences found short term (< 6 months) between oral NSAIDs and topical formulations. Topical NSAIDs were gastroprotective but had higher risk of application site dryness.

Rating: 1a

Pétursson H. The benzodiazepine withdrawal syndrome. *Addiction.* 1994;89:1455-9.

PMID: 7841856

Rating: 5b

Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol Clin.* 2000 Oct;30(5):263-88.

These data suggest that hemodynamic responses to pain reflect simultaneously the sensory, cognitive and affective dimensions of pain, and that the same structure may both respond to pain and participate in pain control.

PMID: 11126640

Rating: 5b

Phillips DP, Barker GE, Eguchi MM. A steep increase in domestic fatal medication errors with use of alcohol and/or street drugs. *Arch Intern Med*. 2008 Jul 28;168(14):1561-6.

RESULTS: The overall FME death rate increased by 360.5% (1983-2004). This increase far exceeds the increase in death rates from adverse effects of medications (33.2%) or from alcohol and/or street drugs (40.9%).

PMID: 18663169

Rating: 4a

Poleshuck EL, Bair MJ, Kroenke K, Damush TM, Tu W, Wu J, Krebs EE, Giles DE. Psychosocial stress and anxiety in musculoskeletal pain patients with and without depression. *Gen Hosp Psychiatry*. 2009;31:116-22.

CONCLUSIONS: Both anxiety and psychosocial stress should be considered in the assessment and treatment of patients with musculoskeletal pain and depression. Tailored, integrated treatments that target the psychosocial needs of patients with pain and depression are needed. In addition to pharmacotherapy, psychotherapy and other behavioral treatments may be especially important for depression complicated by anxiety or psychosocial stress.

PMID: 19269531

Rating: 3a

Pollack MH, Allgulander C, Bandelow B, Cassano GB, Greist JH, Hollander E, Nutt DJ, Okasha A, Swinson RP; World Council of Anxiety. WCA recommendations for the long-term treatment of panic disorder. *CNS Spectr*. 2003 Aug;8(8 Suppl 1):17-30

Selective serotonin reuptake inhibitors have emerged as the most favorable treatment, as they have a beneficial side-effect profile, are relatively safe (even if taken in overdose), and do not produce physical dependency.

PMID: 14767395

Rating: 5a

Portenoy RK, Sciberras A, Eliot L, Loewen G, Butler J, Devane J. Steady-state pharmacokinetic comparison of a new, extended-release, once-daily morphine formulation, Avinza, and a twice-daily controlled-release morphine formulation in patients with chronic moderate-to-severe pain. *J Pain Symptom Manage*. 2002 ;23:292-300.

PMID: 1199719

Rating: 4c

Prager JP, Mackey S, Alexander G, Schwartzman R. Breaking concepts in diagnosis and treatment of complex regional pain syndromes. Program and abstracts of the American Academy of Pain Medicine 23rd Annual Meeting; February 7-10, 2007; New Orleans, Louisiana.

This topic focused on the use of functional brain imaging to look for areas of the brain that are active in response to pain stimuli. Functional brain imaging may represent an excellent opportunity to provide an objective measurement of pain and provide a means to monitor treatment efficacy.

Rating: 10b

Prager J. Four decades of neuromodulation. Program and abstracts of the American Academy of Pain Medicine 23rd Annual Meeting; February 7-10, 2007; New Orleans, Louisiana.

Although there are still not a lot of hard, randomized controlled trial data on the use of neuromodulation for visceral pain, such as for problems involving the intestines, stomach, and pelvic organs, mounting case study evidence suggests a valuable role for neuromodulation in this area.

Rating: 10a

Proctor TJ, Mayer TG, Gatchel RJ, McGeary DD. Unremitting health-care-utilization outcomes of tertiary rehabilitation of patients with chronic musculoskeletal disorders. *J Bone Joint Surg Am*. 2004;86:62-9.

CONCLUSIONS: The results demonstrate that about 25% of patients with a chronic disabling work-related musculoskeletal disorder pursue new health-care services after completing a course of treatment, and this subgroup accounts for a significant proportion of lost worker productivity, unremitting disability payments, and excess health-care consumption.

PMID: 14711947

Rating: 3a

Prommer E. Levorphanol: the forgotten opioid. *Support Care Cancer*. 2007;15:259-64.

CONCLUSION: The long half-life of the drug increases the potential for drug accumulation. Levorphanol has clinical efficacy in neuropathic pain.

Rating; 5c

Pulliam CB, Gatchel RJ, Gardea MA. Psychosocial differences in high risk versus low risk acute low-back pain patients. Journal of Occupational Rehabilitation. 2001 Mar;11(1):43-52.

The current study built upon previous research that predicted with 90.7% accuracy which patients presenting with acute low-back pain go on to develop chronic disability problems.

Publication Type: Case Control Study, 57 cases

PMID: 11706776

Qerama E, Fuglsang-Frederiksen A, Kasch H, Bach FW, Jensen TS. A double-blind, controlled study of botulinum toxin A in chronic myofascial pain. *Neurology.* 2006 Jul 25;67(2):241-5.

Danish Pain Research Center, Aarhus University Hospital, Denmark. erisela@akhphd.au.dk

BACKGROUND: Recent studies have reported a potential analgesic effect of botulinum toxin A (BTXA) in musculoskeletal pain. The present double-blind, randomized, placebo-controlled, parallel clinical trial studied the effect of BTXA on pain from muscle trigger points and on EMG activity at rest and during voluntary contraction. METHODS: Thirty patients with trigger points in the infraspinatus muscles received either 50 units/0.25 mL of BTXA or 0.25 mL of isotonic saline. Baseline measures were determined during a run-in period of 1 week. Outcome measures including local and referred spontaneous pain, pain detection and tolerance thresholds to mechanical pressure, and shoulder movement were assessed at 3 and 28 days after injection. RESULTS: BTXA reduced motor endplate activity and the interference pattern of EMG significantly but had no effect on either pain (spontaneous or referred) or pain thresholds compared with isotonic saline. CONCLUSIONS: The results do not support a specific antinociceptive and analgesic effect of botulinum toxin A.

PMID: 16864815

Rating: 2c

Quisel A, Gill JM, Witherell P. Complex regional pain syndrome: which treatments show promise? *J Fam Pract*. 2005 Jul;54(7):599-603.

Treatments for CRPS type 1 supported by evidence of efficacy and little likelihood for harm are: topical DMSO cream (B), IV bisphosphonates (A) and limited courses of oral corticosteroids (B). Despite some contradictory evidence, physical therapy and calcitonin (intranasal or intramuscular) are likely to benefit patients with CRPS type 1 (B). Due to modest benefits and the invasiveness of the therapies, epidural clonidine injection, intravenous regional sympathetic block with bretylium and spinal cord stimulation should be offered only after careful counseling (B). Therapies to avoid due to lack of efficacy, lack of evidence, or a high likelihood of adverse outcomes are IV regional sympathetic blocks with anything but bretylium, sympathetic ganglion blocks with local anesthetics, systemic IV sympathetic inhibition, acupuncture, and sympathectomy (B).

PMID: 16009087

Rating: 5a

Quisel A, Gill JM, Witherell P. Complex regional pain syndrome underdiagnosed. *J Fam Pract*. 2005 Jun;54(6):524-32.

Complex regional pain syndrome (CRPS) type 1 may be diagnosed by history and physical exam with no further testing. Several different diagnostic criteria have undergone validity testing: the 1993 IASP criteria, Bruehl's criteria, and Veldman's criteria; there is no compelling reason to recommend 1 set of criteria over the others. Some cases of CRPS type 1 may be preventable. Some cases of CRPS type 1 in 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. Some cases of post-fracture CRPS type 1 may be prevented with 500 mg vitamin C daily started upon diagnosis of fracture and continued through healing.

PMID: 15939004

Rating: 5b

Rajagopal, A., et al. Symptomatic Hypogonadism in Male Survivors of Cancer with Chronic Exposure to Opioids. *Cancer*. 2004; Volume 100, Number 4, 851-858.

Rating: 2c

Quality: Low. Total Rating: 1.5. Comment: Does not meet inclusion criteria for evidence-based review.

Ramakrishnan K, Scheid DC. Treatment options for insomnia. *Am Fam Physician*. 2007 Aug 15;76(4)517-26.

Hypnotics generally should be prescribed for short periods only, with the frequency and duration of use customized to each patient's circumstances. Routine use of over-the-counter drugs containing antihistamines should be discouraged. Alcohol has the potential for abuse and should not be used as a sleep aid. Opiates are valuable in pain-associated insomnia. Benzodiazepines are most useful for short-term treatment; however, long-term use may lead to adverse effects and withdrawal phenomena. The better safety profile of the newer-generation nonbenzodiazepines (i.e., zolpidem, zaleplon, eszopidone, and ramelteon) makes them better first-line choices for long-term treatment of chronic insomnia.

Rating: 5b

Raphael, J., et al. Long-term experience with implanted intrathecal drug administration systems for failed back syndrome and chronic mechanical low back pain. *BMC Musculoskeletal Disorders.* 2002; Volume 3, Number 17.

Rating: 2c

Quality: Low. Total Rating: 2.0. Comment: Does not meet inclusion criteria for evidence-based review.

Rauck RL, Wallace MS, Leong MS, Minehart M, Webster LR, Charapata SG, Abraham JE, Buffington DE, Ellis D, Kartzinel R; Ziconotide 301 Study Group. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain*. J Pain Symptom Manage*. 2006;31:393-406.

Slow titration of ziconotide, a nonopioid analgesic, to a low maximum dose resulted in significant improvement in pain and was better tolerated than in two previous controlled trials that used a faster titration to a higher mean dose.

PMID: 16716870

Rating: 2c

This study showed a fairly small effect size but was helpful in determining appropriate dosing.

Rauck RL, Eisenach JC, Jackson K, Young LD, Southern J. Epidural clonidine treatment for refractory reflex sympathetic dystrophy. *Anesthesiology*. 1993 ;79:1163-9.

PMID: 8267190

Rating: 2c

Ray JB, Kalra R. Opioid Alternatives Urged Postoperatively. PAINWeek 2013. Presented September 6, 2013.

Rating: 10a

Reeder CE, Franklin M, Bramley TJ. Current landscape of insomnia in managed care. *Am J Manag Care*. 2007;13:S112-6.

Primary insomnia (not caused by known physical/mental conditions) responds to pharmacologic therapy, while secondary insomnia(resulting from other illnesses, medications, or sleep disorders) responds to pharmacologic and psychologic treatments (cognitive therapy, relaxation techniques, stimulus control).

PMID: 1804187

Rating: 5b

Reeves RR, Parker JD. Somatic dysfunction during carisoprodol cessation: evidence for a carisoprodol withdrawal syndrome. *J Am Osteopath Assoc.* 2003 Feb;103(2):75-80.

Carisoprodol is a commonly used skeletal muscle relaxant with potential for abuse because of its active metabolite, meprobamate, and several reports have suggested that patients abruptly stopping intake of carisoprodol may have a withdrawal syndrome.

PMID: 12622352

Rating: 4c

Reeves RR, Burke RS. Is it time for carisoprodol to become a controlled substance at the federal level? *South Med J*. 2008;101:127-8.

Rating: 5b

Reeves RR, Hammer JS, Pendarvis RO. Is the frequency of carisoprodol withdrawal syndrome increasing? *Pharmacotherapy*. 2007;27:1462-6.

PMID: 17896902

Rating: 4c

Reeves RR, Beddingfield JJ, Mack JE. Carisoprodol withdrawal syndrome. *Pharmacotherapy*. 2004;24:1804-6.

PMID: 15585447

Rating: 4c

Reeves RR, Liberto V. Abuse of combinations of carisoprodol and tramadol. *South Med J.* 2001;94:512-4.

PMID: 11372804

Rating: 4c

Reeves RR, Carter OS, Pinkofsky HB, Struve FA, Bennett DM. Carisoprodol (soma): abuse potential and physician unawareness*. J Addict Dis.* 1999;18:51-6.

PMID: 10334375

Rating: 4b

Reeves RR, Burke RS. Carisoprodol: Abuse Potential and Withdrawal Syndrome. *Curr Drug Abuse Rev*. 2010

PMID: 20088817

Rating: 5b

Reeves RR, Burke RS, Kose S. Carisoprodol: update on abuse potential and legal status. *South Med J*. 2012;105:619-23.

PMID: 23128807

Rating: 5b

Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacovelli G, Henrotin Y, Dacre JE, Gossett C. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet*. 2001 Jan 27;357(9252):251-6.

PMID: 11214126

Rating: 2b

Reichenbach S, Sterchi R, Scherer M, Trelle S, Burgi E, Burgi U, Dieppe PA, Juni P. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med*. 2007 Apr 17;146(8):580-90.

PMID: 17438317

Rating: 1b

Reynoldson JN, Elliott ES, Nelson LA. Ramelteon: A Novel Approach in the Treatment of Insomnia (CE). *Ann Pharmacother.* 2008 Jul 23.

CONCLUSIONS: Ramelteon offers a novel mechanism of action for the treatment of insomnia. Studies support its short- and long-term use in adults and elderly adults for the treatment of primary insomnia characterized by difficulty with sleep initiation.

Rating: 1c

Rho RH, Brewer RP, Lamer TJ, Wilson PR. Complex regional pain syndrome. *Mayo Clin Proc*. 2002 Feb;77(2):174-80.

Physical therapy is the cornerstone and first-line treatment for CRPS. Patients with moderate to severe pain and/or sympathetic dysfunction require regional anesthetic blockade to participate in physical therapy.

PMID: 11838651

Rating: 5b

Ribbers GM, Geurts AC, Stam HJ, Mulder T. Pharmacologic treatment of complex regional pain syndrome I: a conceptual framework. *Arch Phys Med Rehabil.* 2003 Jan;84(1):141-6.

CRPS I is considered a neuropathic pain syndrome with a mixed and time-dependent profile of a regional inflammation, sensitization of primary somatosensory afferents (peripheral sensitization), and sensitization of spinal neurons (central sensitization).

PMID: 12589636

Rating: 5b

Ricci M, Pirotti S, Scarpi E, Burgio M, Maltoni M, Sansoni E, Amadori D. Managing chronic pain: results from an open-label study using MC5-A Calmare® device. *Support Care Cancer*. 2012 Feb;20(2):405-12. doi: 10.1007/s00520-011-1128-6.

PMID: 21394458

Rating: 4c

Richmond J, Hunter D, Irrgang J, Jones MH, Snyder-Mackler L, Van Durme D, Rubin C, Matzkin EG, Marx RG, Levy BA, Watters WC 3rd, Goldberg MJ, Keith M, Haralson RH 3rd, Turkelson CM, Wies JL, Anderson S, Boyer K, Sluka P, St Andre J, McGowan R. American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of osteoarthritis (OA) of the knee. *J Bone Joint Surg Am*. 2010;92:990-3.

This guideline recommends the use of the following for individuals at risk increased GI risk (Age > 60 years, comorbid medical conditions, history of peptic ulcer disease, history of GI bleed, concurrent use of anticoagulants or corticosteroids): Acetaminophen; Topical NSAIDs; Nonselective oral NSAIDs plus gastro-protective agent; Cox-2 agents.

PMID: 20360527

Rating: 6a

Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY, Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis, *Arch Intern Med*. 2003 Jul 14;163(13):1514-22.

PMID: 12860572

Rating: 1b

Rickels K, DeMartinis N, Rynn M, Mandos L. Pharmacologic strategies for discontinuing benzodiazepine treatment. *J Clin Psychopharmacol.* 1999;19:12S-16S.

PMID: 10587279

Rating; 5b

Ringer R, Wertli M, Bachmann LM, Buck FM, Brunner F. Concordance of qualitative bone scintigraphy results with presence of clinical complex regional pain syndrome 1: meta-analysis of test accuracy studies. *Eur J Pain.* 2012;16:1347-56.

PMID: 22473897

Rating: 1c

Robbins W, Clinical applications of capsaicinoids, *Clin J Pain*. 2000 Jun;16(2 Suppl):S86-9.

PMID: 10870746

Rating: 5c

The study found that seven out of ten patients who suffered from debilitating improved by at least 50 percent after being treated by creams with capsaicin concentrates of five percent to ten percent. In the UCSF study, however, patients were able to tolerate the burning because they were given regional anesthesia before the capsaicin was administered. The role of the anesthesia in promoting the effects of
the capsaicin has not been determined. Patients also took morphine to curb burning in the days following treatment, as the burning could last up to five days. Researchers were concerned that high dosages of capsaicin could affect the patients' abilities to sense extreme temperatures and pain,
therefore increasing their chances for further injuries.

Roberts LJ, Finch PM, Pullan PT, Bhagat CI, Price LM. Sex hormone suppression by intrathecal opioids: a prospective study. *Clin J Pain*. 2002 ;18:144-8.

CONCLUSIONS: Administration of intrathecal opioids may result in hypogonadotrophic hypogonadism. As part of the consent for therapy process, patients should be informed about this effect and its management.

PMID: 12048415

Rating: 4c

Roberts LJ, Price L, Hadlow NC, Pullan PT. Hypogonadism in patients treated with intrathecal morphine. *Clin J Pain*. 2000;16:251-4.

CONCLUSIONS: Hypogonadotrophic hypogonadism is a common complication of intrathecal opioid therapy in both men and women.

PMID: 11014399

Rating: 3c

Roberts, L. J., et al. Outcome of intrathecal opioids in chronic non-cancer pain *European Journal of Pain.* 2001; Number 5: 353-361.

Rating: 5c

Quality: N/A. Total Rating: N/A. Comment: Does not meet inclusion criteria for evidence-based review.

Robertson VJ, Baker KG. A review of therapeutic ultrasound: effectiveness studies. *Phys Ther.* 2001 Jul;81(7):1339-50.

CONCLUSION: There was 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.

PMID: 11444997

Rating: 1b

Robinson JP, Fulton-Keohe D, Martin C, Franklin GM. Outcomes of Pain Center Treatment in Washington State Workers' Compensation. *Am J Ind Med* 2001;227-236.

CONCLUSIONS: There was no evidence that pain center treatment alters 2-year time loss status of already disabled workers. Crude comparison showed that odds of receiving time loss payments was lower in treated than in untreated group (OR=0.83, 95% C.I.=0.68-1.00). Apparent advantage of treated group was due to confounders, since pain centers enroll patients with more favorable prognoses (younger, female, less chronic)

Publication Type: Case Control Study, 2032 cases

Rating: 4b

Robinson JP, Fulton-Kehoe D, Franklin GM, Wu R, Multidisciplinary pain center outcomes in Washington State Workers' Compensation, *J Occup Environ Med*. 2004 May;46(5):473-8.

We conducted this study to evaluate the clinical and disability status of injured workers 4.6 years after undergoing multidisciplinary pain center evaluation, comparing subjects who received treatment to subjects who were evaluated only. Three hundred injured workers were selected for a telephone survey. At 4.6 years follow up, there was no evidence that pain center treatment affects either disability status or clinical status of injured workers.

PMID: 15167396

Rating: 4b

Robson PJ. Therapeutic potential of cannabinoid medicines. *Drug Test Anal.* 2014 Jan-Feb;6(1-2):24-30. doi: 10.1002/dta.1529.

PMID: 24006213

Rating: 5b

Rodriguez-Moreno J, Ruiz-Martin JM, Mateo-Soria L, Rozadilla A, Roig-Escofet D. Munchausen's syndrome simulating reflex sympathetic dystrophy. *Ann Rheum Dis.* 1990 Dec;49(12):1010-2.

PMID: 2270960

Rating: 11c

Rome JD, Townsend CO, Bruce BK, Sletten CD, Luedtke CA, Hodgson JE. Chronic noncancer pain rehabilitation with opioid withdrawal: comparison of treatment outcomes based on opioid use status at admission. *Mayo Clin Proc*. 2004 Jun;79(6):759-68.

RESULTS: More than one third of patients (135/356) were taking opioids daily at admission. At completion of the program, all but 3 of the 135 patients had successfully discontinued opioid treatment. Significant improvement was noted at discharge for all outcome variables assessed regardless of opioid status at admission.

PMID: 15182090

Rating: 4b

Note: This was primarily a female, non-workers' compensation population.

Rooks DS. Fibromyalgia treatment update. *Curr Opin Rheumatol*. 2007 Mar;19(2):111-7.

FINDINGS: Recent studies examining the efficacy of two serotonin and norepinephrine-reuptake inhibitors--duloxetine and milnacipran--and the anticonvulsant pregabalin are encouraging. Studies evaluating different forms of exercise continue to support the belief that increased physical activity is an essential component of any treatment plan for the patient with fibromyalgia.

PMID: 17278924

Rating: 1b

Rooks DS, Gautam S, Romeling M, Cross ML, Stratigakis D, Evans B, Goldenberg DL, Iversen MD, Katz JN. Group Exercise, Education, and Combination Self-management in Women With Fibromyalgia: A Randomized Trial. *Arch Intern Med*. 2007 Nov 12;167(20):2192-200.

CONCLUSIONS: Progressive walking, simple strength training movements, and stretching activities improve functional status, key symptoms, and self-efficacy in women with fibromyalgia actively being treated with medication. The benefits of exercise are enhanced when combined with targeted self-management education.

PMID: 17998491

Rating: 2b

Progressive walking, simple strength training, and stretching improved functional status, key symptoms, and self-efficacy in women with fibromyalgia actively treated with medication, according to the results of a randomized controlled trial reported in the November 12 issue of the Archives of Internal Medicine.

Rosenquist RW, Rosenberg J; United States Veterans Administration. Postoperative pain guidelines. *Reg Anesth Pain Med*. 2003 Jul-Aug;28(4):279-88.

A table, which provides a menu of analgesic choices organized by specific operation, was constructed.

PMID: 12945020

Rating: 5c

Rosenstock J, Hollander P, Gadde KM, Sun X, Strauss R, Leung A; OBD-202 Study Group. A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients. *Diabetes Care*. 2007;30:1480-6.

CONCLUSIONS: Topiramate CR treatment produced significant weight loss and meaningful improvements in A1C and blood pressure in obese patients with type 2 diabetes treated with diet and exercise or in combination with metformin. However, the central nervous system and psychiatric adverse event profile of topiramate CR makes it unsuitable for the treatment of obesity and diabetes.

PMID: 17363756

Rating: 2b

Roth SH, Fuller P. Diclofenac topical solution compared with oral diclofenac: a pooled safety analysis. *J Pain Res*. 2011;4:159-67.

The most common AE with TDiclo was dry skin at the application site (24.1% vs. 1.9% with ODiclo).

PMID: 21811391

Rating: 2c

Rother M, Lavins BJ, Kneer W, Lehnhardt K, Seidel EJ, Mazgareanu S. Efficacy and safety of epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: multicentre randomised controlled trial. *Ann Rheum Dis*. 2007;66:1178-83.

RESULTS: The mean WOMAC pain subscale scores in the intent to treat population were reduced by 18.2, 20.3 and 9.9 in the IDEA-033, celecoxib and placebo groups, respectively, and the physical function subscale score by 14.6, 16.6 and 10.2, respectively.

PMID: 1736340

Rating: 2c

Roy-Byrne PP, Davidson KW, Kessler RC, Asmundson GJ, Goodwin RD, Kubzansky L, Lydiard RB, Massie MJ, Katon W, Laden SK, Stein MB. Anxiety disorders and comorbid medical illness. *Gen Hosp Psychiatry*. 2008;30:208-25

CONCLUSIONS: Emerging data offer a strong argument for the role of anxiety in medical illness and suggest that anxiety disorders rival depression in terms of risk, comorbidity and outcome.

PMID: 18433653

This article discusses the role of anxiety in chronic pain.

Rating: 5b

Rozenfeld V, Crain JL, Callahan AK.Possible augmentation of warfarin effect by glucosamine-chondroitin. *Am J Health Syst Pharm*. 2004 Feb 1;61(3):306-7.

PMID: 14986566

Rating: 5b

Ruane R, Griffiths P, Glucosamine therapy compared to ibuprofen for joint pain, *Br J Community Nurs*. 2002 Mar;7(3):148-52.

PMID: 11904551

Rating: 1c

Rubinstein A, Watson J. Hypogonadism Risk Higher With Long vs Short-Acting Opioids. American Academy of Pain Medicine (AAPM) 28th Annual Meeting: Abstract 229. Presented February 24, 2012.

Men treated with long-acting opioids have a higher risk of developing hypogonadism compared with those receiving short-acting formulations, a new study suggests. This retrospective study, included 81 men aged between 18 and 80 years who had no previous diagnosis of hypogonadism and who were taking a stable, daily dose of opioids for chronic pain. When testosterone levels were compared taking type of opioid into account, the analysis showed that a significantly higher number of men receiving long-acting formulations were hypogonadal compared with men receiving short-acting formulations (74% vs 34%; $P < .001$). After controlling for dose (converted to morphine standardized equivalents) and body mass index (BMI), patients receiving long-acting opioids had 4.78 times greater odds of becoming hypogonadal than patients receiving short-acting opioids ($P = .008$). A hypothesis for why short-acting opioids might be less harmful is that their serum levels fluctuate and at certain times of day when the drug level is low and coincides with the cyclical LH burst, testosterone is produced.

Rating: 10b

Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*. 2005 Jul 20;(3):CD005454.

CONCLUSIONS: Antidepressants are effective for a variety of neuropathic pains. The best evidence available is for amitriptyline. There are only limited data for the effectiveness of SSRIs.

PMID: 16034979

Rating: 1a

Saarto T, Wiffen P. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*. 2007 Oct 17;(4):CD005454

CONCLUSIONS: There is still limited evidence for the role of SSRIs.

PMID: 17943857

Review: 1a

Sachs CJ. Oral analgesics for acute nonspecific pain. *Am Fam Physician*. 2005 Mar 1;71(5):913-8.

The safest NSAID is ibuprofen in doses of 400 mg.

PMID: 15768621

Rating: 5b

Sahin F, Yilmaz F, Kotevoglu N, Kuran B. Efficacy of salmon calcitonin in complex regional pain syndrome (type 1) in addition to physical therapy. *Clin Rheumatol*. 2005 Jun 25.

We can conclude that calcitonin does not make any favourable contribution in the treatment of patients with acute CRPS 1; physical therapy combined with only a simple analgesic is an efficient means of therapy.

PMID: 15980934

Rating: 2b

Salerno SM, Browning R, Jackson JL, The effect of antidepressant treatment on chronic back pain: a meta-analysis, *Arch Intern Med*. 2002 Jan 14;162(1):19-24.

CONCLUSION: Antidepressants are more effective than placebo in reducing pain severity but not functional status in chronic back pain.

PMID: 11784215

Salinsky M, Storzbach D, Munoz S. Cognitive effects of pregabalin in healthy volunteers: a double-blind, placebo-controlled trial. *Neurology*. 2010 Mar 2;74(9):755-61.

RESULTS: Thirty subjects completed the study (94%). CONCLUSION: At conventional doses and titration, pregabalin induced mild negative cognitive effects and neurotoxicity complaints in healthy volunteers.

PMID: 20194915

Rating: 2b

SAMHSA (Substance Abuse and Mental Health Services Administration). Center for Behavioral Health Statistics and Quality. (October 27, 2011). The DAWN Report: ED Visits Involving the Muscle Relaxant Carisoprodol. Rockville, MD.

- The number of carisoprodol-related ED visits involving misuse or abuse doubled from 15,830 visits in 2004 to 31,763 visits in 2009
- The number of carisoprodol-related ED visits involving misuse or abuse by patients aged 50 or older tripled between 2004 and 2009 (from 2,070 to 7,115 visits)
- The majority of ED visits involving carisoprodol also involved other pharmaceuticals (77 percent); the most common combinations involved narcotic pain relievers (55 percent) and benzodiazepines (47 percent)
- Of all the carisoprodol visits classified as misuse or abuse, one third (35 percent) of the visits required hospitalization

Rating: 8a

Sanders SH, Harden RN, Vicente PJ. Evidence-Based Clinical Practice Guidelines for Interdisciplinary Rehabilitation of Chronic Nonmalignant Pain Syndrome Patients. World Institute of Pain, *Pain Practice*, Volume 5, Issue 4, 2005 303–315.

The current guidelines recommend interdisciplinary-focused rehabilitation, which is goal-directed and time-limited. Emphasis is placed on educating patients in active self-management techniques that stress maximizing function. Integrated treatment involving medical, psychological/behavioral, physical/occupational therapy, and disability/vocational interventions are recommended on an outpatient basis whenever clinically possible. Note: This issue of this journal was not accepted into Medline, and therefore it is not part of the primary evidence based used for ODG, but it includes a helpful reference list.

Per Andrew Brylowski, M.D.:
AMA guides fifth edition page 567 defines chronic pain syndrome (CPS) as: "Although not official nomenclature, it is frequently used (chronic pain syndrome) to describe an individual who is markedly impaired by chronic pain with substantial psychological overlay. Chronic pain syndrome is largely a behavioral syndrome that affects a minority of those with chronic pain.

Per ODG Reviewers:
... the definition of chronic pain syndrome remains controversial. The challenge for a treatment guideline is to find an operational definition that helps reviewers and treating providers to define whether or not someone has the condition, or not. In that sense, the 5th edition of the Guides may not be as helpful as the 4th edition. In the 4th edition, on pp. 308-309, there is a definition of "8 Ds," of which 4 or more are considered to reliably define the CPS. With regards to the Sanders article… as the Abstract points out, this is the third iteration of this "guideline," and contains updated references… it is published in a relatively low-impact journal of questionable peer review (an uncertain indexing in Index Medicus). This is a "pragmatic guideline," based on a highly selective review of the pain literature. ... it does not focus on chronic pain treatment in workers' compensation, which leaves the usual problems of subjectivity associated with the outcomes.

Sator-Katzenschlager SM, Michalek-Sauberer A. P-Stim auricular electroacupuncture stimulation device for pain relief. *Expert Rev Med Devices*. 2007 Jan;4(1):23-32.

PMID: 17187468

Rating: 5c

Scarano VR, Jankovic J. Post-traumatic movement disorders: effect of the legal system on outcome. *J Forensic Sci*. 1998;43:334-9.

PMID: 9544540

Rating: 4b

Schaafsma F, Schonstein E, Whelan KM, Ulvestad E, Kenny DT, Verbeek JH. Physical conditioning programs for improving work outcomes in workers with back pain. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD001822. doi: 10.1002/14651858.CD001822.pub2. Review.

RESULTS: Thirty-seven references, reporting on 23 RCTs (3676 workers) were included, 13 of which had a low risk of bias. In 14 studies, physical conditioning programs were compared to usual care. In workers with acute back pain, there was no effect on sickness absence. For workers with subacute back pain, we found conflicting results, but subgroup analysis showed a positive effect of interventions with workplace involvement. In workers with chronic back pain, pooled results of five studies showed a small effect on sickness absence at long-term follow-up (SMD: -0.18 (95% CI: -0.37 to 0.00)). In workers with chronic back pain, physical conditioning programs were compared to other exercise therapy in six studies, with conflicting results. The addition of cognitive behavioural therapy to physical conditioning programs was not more effective than the physical conditioning alone.

AUTHORS' CONCLUSIONS: The effectiveness of physical conditioning programs in reducing sick leave when compared to usual care or than other exercises in workers with back pain remains uncertain. In workers with acute back pain, these programs probably have no effect on sick leave, but there may be a positive effect on sick leave for workers with subacute and chronic back pain. Workplace involvement might improve the outcome. Better understanding of the mechanism behind physical conditioning programs and return-to-work is needed to be able to develop more effective interventions.

Rating: 1b

Schears RM. Nonbenzodiazepine hypnosedatives. In: Emergency Medicine: A Comprehensive Study Guide, 6th ed. McGraw-Hill 2004.

Rating: 9b

Schjerning Olsen AM, Fosbøl EL, Lindhardsen J, Folke F, Charlot M, Selmer C, Lamberts M, Bjerring Olesen J, Køber L, Hansen PR, Torp-Pedersen C, Gislason GH. Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction: A Nationwide Cohort Study. *Circulation*. 2011 May 9. [Epub ahead of print]

Of the 83,677 patients included, 42.3% received NSAIDs during follow-up. Conclusions- Even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent MI in patients with prior MI.

PMID: 21555710

Rating: 3a

Schmidt S, Grossman P, Schwarzer B, Jena S, Naumann J, Walach H. Treating fibromyalgia with mindfulness-based stress reduction: results from a 3-armed randomized controlled trial. *Pain.* 2011 Feb;152(2):361-9. Epub 2010 Dec 13.

In conclusion, primary outcome analyses did not support the efficacy of Mindfulness-based stress reduction (MBSR) in fibromyalgia, although patients in the MBSR arm appeared to benefit most.

PMID: 21146930

Rating: 2b

Schmitt R, Gazalle FK, Lima MS, Cunha A, Souza J, Kapczinski F. The efficacy of antidepressants for generalized anxiety disorder: a systematic review and meta-analysis. *Rev Bras Psiquiatr*. 2005; 27:18-24.

RESULTS: Antidepressants (imipramine, venlafaxine and paroxetine) were found to be superior to placebo in treating generalized anxiety disorder. The calculated number needed to treat for antidepressants in generalized anxiety disorder was 5.15.

PMID: 15867979

Rating: 1c

Schneider-Helmert D. Do we need polysomnography in insomnia? *Praxis* (Bern 1994). 2003 Nov 26;92(48):2061-6.

Special problems arise in chronic non-organic pain. It is clear from all these aspects that PSG is indispensable in insomnia.

PMID: 14694544

Rating: 5b

Schneier FR. Clinical practice. Social anxiety disorder. *N Engl J Med*. 2006;355:1029-36.

PMID: 16957148

Rating: 5c

Schnitzer TJ, Ferraro A, Hunsche E, Kong SX. A comprehensive review of clinical trials on the efficacy and safety of drugs for the treatment of low back pain. *J Pain Symptom Manage*. 2004 Jul;28(1):72-95.

Available evidence supported the effectiveness of non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) in acute and chronic LBP, of muscle relaxants in acute LBP, and of antidepressants in chronic LBP; safety results were heterogeneous.

PMID: 15223086

Rating: 1b

Scholmerich J. Nonsteroidal anti-inflammatory drugs versus selective COX-2 inhibitors in the upper gastrointestinal tract. *J Cardiovasc Pharmacol*. 2006;47 Suppl 1:S67-71.

Considering the current controversy regarding cardiovascular events, there is no major reason to prefer coxibs to conventional NSAID plus PPI in patients needing long-term treatment.

PMID: 16785832

Rating: 5c

Schonstein E, Kenny D, Keating J, Koes B, Herbert RD. Physical conditioning programs for workers with back and neck pain: a cochrane systematic review. *Spine.* 2003 Oct 1;28(19):E391-5

CONCLUSION: Physical conditioning programs that incorporate a cognitive-behavioral approach reduce the number of sick days for workers with chronic back pain when compared to usual care.

PMID: 14520051

Rating: 1b

Schultz IZ, Crook J, Berkowitz J, Milner R, Meloche GR, Lewis ML. A Prospective Study of the Effectiveness of Early Intervention with High-risk Back-injured Workers-A Pilot Study. *J Occup Rehabil.* 2008 Jun;18(2):140-51. Epub 2008 Apr 11.

Conclusion: Multimodal Early Intervention in the workers' compensation case management context is likely effective for workers with sub-acute back pain who are at high risk of occupational disability.

PMID: 18404361

Rating: 3b

Schürmann M, Gradl G, Wizgal I, Tutic M, Moser C, Azad S, Beyer A. Clinical and physiologic evaluation of stellate ganglion blockade for complex regional pain syndrome type I. *Clin J Pain*. 2001;17:94-100.

PMID: 11289093

Rating: 4c

Schürmann M, Zaspel J, Löhr P, Wizgall I, Tutic M, Manthey N, Steinborn M, Gradl G. Imaging in early posttraumatic complex regional pain syndrome: a comparison of diagnostic methods. *Clin J Pain.* 2007;23:449-57.

PMID: 17515744

Rating: 4b

Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain*. 2009 Dec 15;147(1-3):107-15.

The results of this study warrant a larger randomized placebo controlled trial using higher doses of ketamine and a longer follow-up period.

PMID: 19783371

Rating: 2c

See S, Ginzburg R. Skeletal muscle relaxants. *Pharmacotherapy*. 2008; 28:207-13.

Therefore, the choice of a skeletal muscle relaxant should be based on its adverse-effect profile, tolerability, and cost.

PMID: 18225966

Rating 5c

See S, Ginzburg R. Choosing a skeletal muscle relaxant. *Am Fam Physician*. 2008 Aug 1;78(3):365-70.

The most commonly prescribed antispasmodic agents are carisoprodol, cyclobenzaprine, metaxalone, and methocarbamol. Despite their popularity, skeletal muscle relaxants should not be the primary drug class of choice for musculoskeletal conditions.

PMID: 18711953

Rating: 5b

Sengupta K, Alluri KV, Satish AR, Mishra S, Golakoti T, Sarma KV, Dey D, Raychaudhuri SP. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin(R) for treatment of osteoarthritis of the knee. *Arthritis Res Ther*. 2008 Jul 30;10(4):R85. [Epub ahead of print]

CONCLUSION: 5-Loxin(R) reduces pain and improves physical functioning significantly in OA patients; and it is safe for human consumption.

PMID: 18667054

Rating: 2c

An enriched extract of the 'Indian Frankincense' herb Boswellia serrata has been proven to reduce the symptoms of osteoarthritis. The same authors have previously tested the safety of their remedy in animal experiments. They say that, "In this study, the compound was shown to have no major adverse effects in our osteoarthritis patients. It is safe for human consumption and even for long-term use".

Serpell MG; Neuropathic pain study group. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. *Pain*. 2002;99:557-66.

This study shows that gabapentin reduces pain and improves some quality-of-life measures in patients with a wide range of neuropathic pain syndromes.

PMID: 12406532

Rating: 2b

Severeijns R; Vlaeyen JW; van den Hout MA; Weber WE. Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *Clinical Journal of Pain.* 01-Jun-2001; 17(2): 165-72.

Publication Type: Case Control Study, 211 cases

PMID: 11444718

This was a case report of orphenadrine dependence.

Shariatmadari ME. Letter: Orphenadrine dependence. Br Med J. 1975;3:486. Rating: 11b

Sharma A, Williams K, Raja SN. Advances in treatment of complex regional pain syndrome: recent insights on a perplexing disease. *Curr Opin Anaesthesiol*. 2006;19:566-72.

SUMMARY: Enhanced insight into the pathophysiology of chronic regional pain syndrome has modified current clinical practice and the focus of research. Certain 'standard' therapeutic options for chronic regional pain syndrome have failed the test of time while others have prevailed.

PMID: 16960493

Rating: 5c

Shell W, Bullias D, Charuvastra E, May LA, Silver DS. A Randomized, Placebo-Controlled Trial of an Amino Acid Preparation on Timing and Quality of Sleep. *Am J Ther.* 2009 May 15. [Epub ahead of print]

An amino acid preparation containing both GABA and 5-hydroxytryptophan reduced time to fall asleep, decreased sleep latency, increased the duration of sleep, and improved quality of sleep.

PMID: 19417589

Rating: 2c

Conflict of interest. There were only 18 patients total. No description was given for the actual sleep disorder. This can't be applied overall to any patients because no diagnoses are given.

Sherman RA, Karstetter KW, Damiano M, Evans CB. Stability of temperature asymmetries in reflex sympathetic dystrophy over time and changes in pain. *Clin J Pain*. 1994;10:71-7.

PMID: 8193447

Rating: 4c

Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. *Eur J Clin Pharmacol.* 2008 Oct;64(10):935-51.

PMID: 18679668

Rating: 1a

Sibille KT, Langaee T, Burkley B, Gong Y, Glover TL, King C, Riley JL 3rd, Leeuwenburgh C, Staud R, Bradley LA, Fillingim RB. Chronic pain, perceived stress, and cellular aging: an exploratory study. *Mol Pain.* 2012 Feb 12;8:12.

The chronic pain/high stress group had significantly shorter telomere length compared to the no pain/low stress group.

PMID: 22325162

Rating: 3c

Siddall, P., et al. The efficacy of Intrathecal Morphine and Clonidine in the Treatment of Pain After Spinal Cord Injury. *Anesh. Analg*, 2000; Number 91:1493-8.

Rating: 2b

Quality: Intermediate. Total Rating: 7.5. Comment: 15 patients were divided into research groups. Found that intrathecal clonidine alone did not perform better than placebo.

Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY, Dahan A. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain.* 2009 Oct;145(3):304-11.

In conclusion, in a population of mostly chronic CRPS-1 patients with severe pain at baseline, a multiple day ketamine infusion resulted in significant pain relief without functional improvement.

PMID: 19604642

Rating: 2b

Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. *Basic Clin Pharmacol Toxicol*. 2005 Jun;96(6):399-409.

In conclusion, antidepressants represent useful tools in neuropathic pain treatment and must still be considered as first line treatments of neuropathic pain.

PMID: 15910402

Rating: 5a

Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain*. 1999 Dec;83(3):389-400.

In central pain, NNT was 2.5 for tricyclics and 3. 4 for carbamazepine, whereas selective serotonin reuptake inhibitors, mexiletine and dextromethorphan were inactive.

PMID: 10568846

Rating: 1b

Singh HP, Davis TR. The effect of short-term dependency and immobility on skin temperature and colour in the hand. *J Hand Surg Br*. 2006;31:611-5.

PMID: 17034912

Rating: 4c

Singh G, Willen SN, Boswell MV, Janata JW, Chelimsky TC. The value of interdisciplinary pain management in complex regional pain syndrome type I: a prospective outcome study*. Pain Physician*. 2004;7:203-9.

PMID: 16868593

Rating: 4c

Skouen JS, Grasdal AL, Haldorsen EM, Ursin H. Relative cost-effectiveness of extensive and light multidisciplinary treatment programs versus treatment as usual for patients with chronic low back pain on long-term sick leave: randomized controlled study. *Spine.* 2002 May 1;27(9):901-9; discussion 909-10.

RESULTS: In men significantly better results for full return to work were found for the light multidisciplinary treatment compared with treatment as usual, but no differences were found between extensive multidisciplinary treatment and treatment as usual. No significant differences between any of the two multidisciplinary treatment programs and the controls were found for women.

PMID: 11979157

Rating: 2b

Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain*. 2008 Feb;9(2):164-73.

As nabilone improved symptoms and was well-tolerated, it may be a useful adjunct for pain management in fibromyalgia.

PMID: 17974490

Rating: 2c

Future studies with a longer duration of treatment and a stable dose are still needed, they add. The medication's costs — $4000 a year in Canada — may be prohibitive to some patients, they observe. 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, Dr. Kissel said. In addition, the dropout patients were not included in an intention-to-treat analysis, which would have resulted in a lower improvement rate.

Smeets RJ, Vlaeyen JW, Hidding A, Kester AD, van der Heijden GJ, van Geel AC, Knottnerus JA. Active rehabilitation for chronic low back pain: Cognitive-behavioral, physical, or both? First direct post-treatment results from a randomized controlled trial. *BMC Musculoskelet Disord*. 2006 Jan 20;7(1):5.

CONCLUSIONS: All three active treatments were effective in comparison to no treatment, but no clinically relevant differences between the combined and the single component treatments were found.

PMID: 16426449

Rating: 2a

Smith DE, Landry MJ. Benzodiazepine dependency discontinuation: focus on the chemical dependency detoxification setting and benzodiazepine-polydrug abuse. *J Psychiatr Res.* 1990;24:145-56

PMID: 1980693

Rating: 5b

Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. A single-question screening test for drug use in primary care. *Arch Intern Med*. 2010 Jul 12;170(13):1155-60.

PMID: 20625025

Rating: 3b

Smith MJ, Cobia DJ, Wang L, Alpert KI, J Cronenwett W, B Goldman M, Mamah D, Barch DM, Breiter HC, Csernansky JG. Cannabis-Related Working Memory Deficits and Associated Subcortical Morphological Differences in Healthy Individuals and Schizophrenia Subjects. *Schizophr Bull*. 2013 Dec 15.

PMID: 24342821

Rating: 3b

Smith TL, Blum K, Callahan MF, DiNubile NA, Chen TJ, Waite RL. H-Wave induces arteriolar vasodilation in rat striated muscle via nitric oxide-mediated mechanisms. *J Orthop Res.* 2009 Sep;27(9):1248-51. doi: 10.1002/jor.20851.

PMID: 19204915

Rating: 5c

Smith TL, Callahan MF, Blum K, Dinubile NA, Chen TJ, Waite RL. H-Wave® effects on blood flow and angiogenesis in longitudinal studies in rats. *J Surg Orthop Adv.* 2011 Winter;20(4):255-9.

PMID: 22381420

Rating: 5c

Soares A, Andriolo RB, Atallah AN, da Silva EM. Botulinum toxin for myofascial pain syndromes in adults. *Cochrane Database Syst Rev*. 2014 Jul 25;7:CD007533. doi: 10.1002/14651858.CD007533.pub3.

PMID: 25062018

Rating: 1a

Solak O, Turna A, Pekcolaklar A, Metin M, Sayar A, Solak O, Gurses A. Transcutaneous electric nerve stimulation for the treatment of postthoracotomy pain: a randomized prospective study. *Thorac Cardiovasc Surg*. 2007 Apr;55(3):182-5.

CONCLUSION: This study demonstrated that TENS provided a better pain relief and comfort compared to PCA from the fourth postoperative day onwards, and this pain-reducing effect continued for at least two months postoperatively.

PMID: 17410506

Rating: 2c

Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, Avorn J, Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults, *Circulation*. 2004 May 4;109(17):2068-73. Epub 2004 Apr 19.

CONCLUSIONS: In this study, current rofecoxib use was associated with an elevated relative risk of AMI compared with celecoxib use and no NSAID use. Dosages of rofecoxib >25 mg were associated with a higher risk than dosages < or =25 mg. The risk was elevated in the first 90 days of use but not thereafter.

PMID: 15096449

Rating: 4a

Sommer HM. The Patient in Jeopardy: How the Low Back Pain Patient Becomes Disabled. *Occupational Medicine* 1998;(13)1:23-31.

Dr. Sommer divides the low back pain episode into four stages that can lead to patient disablement.

Publication Type: Review

PMID: 11444718

Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). *Cochrane Database Syst Rev*. 2008;(1):CD001765.

CONCLUSIONS: SSRIs are more effective than placebo for OCD, at least in the short-term, although there are differences between the adverse effects of individual SSRI drugs. The longer term efficacy and tolerability of different SSRI drugs for OCD has yet to be established.

PMID: 18253995

Rating: 1c

Spence SH, Sharpe L, Newton-John T, Champion D. Effect of EMG biofeedback compared to applied relaxation training with chronic, upper extremity cumulative trauma disorders. *Pain.* 1995 Nov;63(2):199-206.

The strongest short-term treatment benefits were shown by patients receiving applied relaxation training on measures of pain, distress, interference in daily living, depression and anxiety. By 6-month follow-up, differences between treatment groups were no longer evident.

PMID: 8628585

Rating: 2c

Spruce MC, Potter J, Coppini DV. The pathogenesis and management of painful diabetic neuropathy: a review. *Diabet Med*. 2003 Feb;20(2):88-98.

Emerging theories suggest that early dysaesthesia associated with painful neuropathy may act as a marker for the development of the 'at risk' foot, allowing preventative clinical strategies to be undertaken.

PMID: 12581259

Rating: 5c

Staal JB, de Bie R, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev*. 2008;(3):CD001824.

RESULTS: 18 trials (1179 participants) were included in this updated review. CONCLUSIONS: There is insufficient evidence to support the use of injection therapy in subacute and chronic low-back pain.

PMID: 18646078

Rating: 1b

Stacey BR, Dworkin RH, Murphy K, Sharma U, Emir B, Griesing T. Pregabalin in the Treatment of Refractory Neuropathic Pain: Results of a 15-Month Open-Label Trial. *Pain Med.* 2008 Mar 11.

Conclusions. These results suggest that pregabalin may be beneficial in patients with neuropathic pain who have had an unsatisfactory response to treatment with other medications.

PMID: 18346060

Rating: 4c

Stanos S, Houle TT. Multidisciplinary and interdisciplinary management of chronic pain. *Phys Med Rehabil Clin N Am.* 2006 May;17(2):435-50, vii.

Multidisciplinary and interdisciplinary pain management programs incorporate a biopsychosocial model in assessing and treating pain and result in pain reduction, improved quality of life, and psychosocial functioning.

Rating: 5c

Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain*. 1995 Oct;63(1):127-33.

The term sympathetically maintained pain (SMP) was also evaluated and considered to be a variable phenomenon associated with a variety of disorders, including CRPS types I and II.

PMID: 8577483

Rating: 5a

Stanton-Hicks M. Complex Regional Pain Syndrome. In: Warfield CA, Bajwa JH. Principles and Practice of Pain Medicine. 2nd ed. McGraw-Hill; 2004.

Rating 9a

State of Colorado Department of Labor and Employment, Division of Workers' Compensation. Colorado Rule XVII, Exhibit 7, Complex Regional Pain Syndrome Medical Treatment Guideline. 01/01/06

Complex Regional Pain Syndrome (CRPS Types I and II) describes painful syndromes, which were formerly referred to as Reflex Sympathetic Dystrophy (RSD) and causalgia.

Publication Type: State Treatment Guideline

Rating: 7a

Staiger TO, Gaster B, Sullivan MD, Deyo RA, Systematic review of antidepressants in the treatment of chronic low back pain, *Spine*. 2003 Nov 15;28(22):2540-5

CONCLUSIONS: Based on a small number of studies, tricyclic and tetracyclic antidepressants appear to produce moderate symptom reductions for patients with chronic low back pain. This benefit appears to be independent of depression status. SSRIs do not appear to be beneficial for patients with chronic low back pain. There is conflicting evidence whether antidepressants improve functional status of patients with chronic low back pain.

PMID: 14624092

Rating: 1b

Stanton-Hicks M. Complex regional pain syndrome: manifestations and the role of neurostimulation in its management. *J Pain Symptom Manage*. 2006 Apr;31(4 Suppl):S20-4.

If no response to conventional treatment (e.g., pharmacotherapy) is noted within 12-16 weeks, a more interventional technique such as spinal cord stimulation (SCS) should be used.

PMID: 16647591

Rating: 5b

Stegmann JU, Weber H, Steup A, Okamoto A, Upmalis D, Daniels S. The efficacy and tolerability of multiple-dose tapentadol immediate release for the relief of acute pain following orthopedic (bunionectomy) surgery. *Curr Med Res Opin*. 2008 Oct 10. [Epub ahead of print]

CONCLUSIONS: The study results suggest improved gastrointestinal tolerability of tapentadol IR 50 mg compared with oxycodone at a dose showing comparable efficacy.

PMID: 18851776

Rating: 2b

Stein DJ, Bandelow B, Hollander E, Nutt DJ, Okasha A, Pollack MH, Swinson RP, Zohar J; World Council of Anxiety. WCA Recommendations for the long-term treatment of posttraumatic stress disorder. *CNS Spectr*. 2003 Aug;8(8 Suppl 1):31-9.

Only SSRIs have been proven effective and safe in long-term randomized controlled trials. Current guidelines from the Expert Consensus Panel for PTSD recommend treatment of chronic PTSD for a minimum of 12-24 months.

PMID: 14767396

Rating: 5a

Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis.* 2005 Nov 15;41(10):1373-406.

PMID: 16231249

Rating: 6b

Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R, Lost productive time and cost due to common pain conditions in the US workforce, *JAMA*. 2003 Nov 12;290(18):2443-54.

The study concluded, “Pain is an inordinately common and disabling condition in the US workforce. Most of the pain-related lost productive time occurs while employees are at work and is in the form of reduced performance.”

PMID: 14612481

Rating: 4b

Straus MM, Ghitza UE, Tai B. Preventing deaths from rising opioid overdose in the US - the promise of naloxone antidote in community-based naloxone take-home programs. Subst Abuse Rehabil. 2013; 2013.

PMID: 24273417

Rating: 5c

Stuckey SJ, Jacobs A, Goldfarb J. EMG biofeedback training, relaxation training, and placebo for the relief of chronic back pain. *Percept Mot Skills*. 1986 Dec;63(3):1023-36.

Relaxation-trained subjects showed significant change on eight of the 14 possible comparisons for each treatment condition. EMG biofeedback training showed significant favorable results in only one condition; the placebo condition showed no significant results. Relaxation training gave better results in reducing EMG and pain, and in increasing relaxation and activity than either EMG biofeedback alone or a placebo condition.

PMID: 2949196

Rating: 2c

Substance Abuse and Mental Health Services Administration. SAMHSA Opioid Overdose Prevention Toolkit. HHS Publication No. (SMA) 1 -4742. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2014 .

PMID:

Rating:

Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. *Arch Intern Med*. 2006;166:2087-93.

CONCLUSIONS: Common mental health disorders and problem drug use are associated with initiation and use of prescribed opioids in the general population. Attention to psychiatric disorders is important when considering opioid therapy.

PMID: 17060538

Rating 3a

Sullivan MD, Edlund MJ, Steffick D, Unützer J. Regular use of prescribed opioids: association with common psychiatric disorders. *Pain*. 2005;119:95-103.

Depressive, anxiety and drug abuse disorders are associated with increased use of regular opioids in the general population. Depressive and anxiety disorders are more common and more strongly associated with prescribed opioid use than drug abuse disorders.

PMID: 16298066

Rating: 3a

Sullivan MJ, Ward LC, Tripp D, French DJ, Adams H, Stanish WD. Secondary prevention of work disability: community-based psychosocial intervention for musculoskeletal disorders. *J Occup Rehabil*. 2005 Sep;15(3):377-92.

RESULTS: In the current sample, 63.7% of participants returned to work within 4 weeks of treatment termination.

PMID: 16119228

Rating: 4b

Sullivan MJ, Adams H, Rhodenizer T, Stanish WD. A psychosocial risk factor--targeted intervention for the prevention of chronic pain and disability following whiplash injury. *Phys Ther*. 2006 Jan;86(1):8-18.

PMID: 16386058

Rating: 2b

Sullivan MJ, Adams H. Psychosocial treatment techniques to augment the impact of physiotherapy interventions for low back pain. *Physiother Can*. 2010 Summer;62(3):180-9. doi: 10.3138/physio.62.3.180.

PMID: 21629595

Rating: 3b

Sundaraj SR, Johnstone C, Noore F, Wynn P, Castro M. Spinal cord stimulation: a seven-year audit. *J Clin Neurosci*. 2005 Apr;12(3):264-70.

CONCLUSION: SCS is an effective treatment in the control of chronic neuropathic pain, particularly in combination with comprehensive medical management within a multidisciplinary pain management centre.

PMID: 15851079

Rating: **Taricco, M., et al. Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review. *Eura Medicophys*. 2006; Volume 42: 5-15.**

Rating: 1c

Quality: N/A. Total Rating: N/A. Comment: Does not meet inclusion criteria for evidence-based review.

Tarner IH, Englbrecht M, Schneider M, van der Heijde DM, Müller-Ladner U. The role of corticosteroids for pain relief in persistent pain of inflammatory arthritis: a systematic literature review. *J Rheumatol Suppl.* 2012 Sep;90:17-20. doi: 10.3899/jrheum.120337.

PMID: 22942324

Rating: 1b

Tassone DM, **Boyce E**, **Guyer J**, **Nuzum D**. **Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clin Ther.* 2007:29:26-48.**

CONCLUSIONS: Pregabalin appears to be an effective therapy in patients with diabetic peripheral neuropathy, postherpetic neuralgia, and adults with refractory partial-onset seizures.

PMID: 17379045

Rating: 5a

Taylor WD, Doraiswamy PM. A Systematic Review of Antidepressant Placebo-Controlled Trials for Geriatric Depression: Limitations of Current Data and Directions for the Future, *Neuropsychopharmacology*. 2004 Sep 1

Large placebo response rates, lack of controlled head to head comparisons, and other methodological design differences make crosstrial comparisons difficult.

PMID: 15340391

Rating: 1b

Taylor RS, Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: A systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. *Eur J Pain*. 2006 Feb;10(2):91-101.

CONCLUSIONS: SCS appears to be an effective therapy in the management of patients with CRPS type I (Level A evidence) and type II (Level D evidence). Moreover, there is evidence to demonstrate that SCS is a cost-effective treatment for CRPS type I.

PMID: 16310712

Rating: 1c

Tembe DV, Dhavale A, Desai H, Mane DN, Raut SK, Dhingra G, Sardesai U, Saoji S, Rohra M, Shinde VG, Padsalge M, Paliwal A, Abbasi K, Devnani P, Papinwar S, Phadke S, Mehta H, Bhailume V. Armodafinil versus Modafinil in Patients of Excessive Sleepiness Associated with Shift Work Sleep Disorder: A Randomized Double Blind Multicentric Clinical Trial. *Neurol Res Int.* 2011;2011:514351.

The study did not demonstrate any difference in efficacy and safety of armodafinil and modafinil.

PMID: 21766023

Rating: 2b

Terkelsen AJ, Bach FW, Jensen TS. Experimental forearm immobilization in humans induces cold and mechanical hyperalgesia*. Anesthesiology*. 2008;109:297-307.

PMID: 18648239

Rating: 5c

Thiese MS, Hughes M, Biggs J. Electrical stimulation for chronic non-specific low back pain in a working-age population: a 12-week double blinded randomized controlled trial. *BMC Musculoskelet Disord.* 2013 Mar 28;14:117. doi: 10.1186/1471-2474-14-117.

PMID: 23537462

Rating: 5b

Thompson JC, Dunbar E, Laye RR. Treatment challenges and complications with ziconotide monotherapy in established pump patients. *Pain Physician*. 2006 Apr;9(2):147-52.

This report describes challenges associated with the decision to convert established pump patients from intrathecal opioid therapy to Ziconotide monotherapy. Inadequate analgesia, adverse medication effects, and opioid withdrawal symptoms can precipitate a stressful situation that may be perceived as dangerous or threatening by patients who are predisposed to anxiety. Screening patients for psychiatric disorders, anxiety-proneness and/or vulnerability to stress should be considered to reduce the risk of treatment complications. A multimodal approach is strongly advocated, including rapid responses of treating physicians and nurses along with strong psychological support.

PMID: 16703976

Rating: 4c

Ticknor CB, Pharmacologic considerations in treating depression: a patient-centered approach*. J Manag Care Pharm.* 2004 Mar;10(2 Suppl):S8-15.

Pain and depression are both regulated by serotonin and norepinephine, and several studies suggest that using dual-action antidepressants may be helpful in patients who have an element of pain to their disorder.

PMID: 15046545

Rating: 5b

Tofferi JK, Jackson JL, O'Malley PG, Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis, *Arthritis Rheum*. 2004 Feb 15;51(1):9-13.

Cyclobenzaprine-treated patients were 3 times as likely to report overall improvement and to report moderate reductions in individual symptoms, particularly sleep.

PMID: 14872449

Rating: 1c

Tomas-Carus P, Häkkinen A, Gusi N, Leal A, Häkkinen K, Ortega-Alonso A. Aquatic training and detraining on fitness and quality of life in fibromyalgia. *Med Sci Sports Exerc.* 2007 Jul;39(7):1044-50.

The present water exercise protocol improved some components of HRQOL, balance, and stair climbing in females with fibromyalgia, but regular exercise and higher intensities may be required to preserve most of these gains.

PMID: 17596770

Rating: 2b

Toth PP, Urtis J. Commonly used muscle relaxant therapies for acute low back pain: a review of carisoprodol, cyclobenzaprine hydrochloride, and metaxalone. *Clin Ther*. 2004;26:1355-67.

Cyclobenzaprine hydrochloride has the most recent and largest clinical trials demonstrating its benefit, but carisoprodol and metaxalone also appear to be effective. However, carisoprodol's usefulness is mitigated by its potential for abuse.

PMID: 15530999

Ranking: 5a

Towheed TE, Anastassiades TP, Shea B, Houpt J, Welch V, Hochberg MC, Glucosamine therapy for treating osteoarthritis, *Cochrane Database Syst Rev*. 2001;(1):CD002946.

PMID: 11279782

Rating: 1b

Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev*. 2006 ;(1):CD004257.

CONCLUSIONS: The evidence to date suggests that NSAIDs are superior to acetaminophen for improving knee and hip pain in people with OA. The size of the treatment effect was modest, and the median trial duration was only six weeks, therefore, additional considerations need to be factored in when making the decision between using acetaminophen or NSAIDs. In OA subjects with moderate-to-severe levels of pain, NSAIDs appear to be more effective than acetaminophen.

PMID: 16437479

Rating: 1c

Towheed TE. Pennsaid therapy for osteoarthritis of the knee: a systematic review and metaanalysis of randomized controlled trials. *J Rheumatol*. 2006 Mar;33(3):567-73.

CONCLUSION: Pennsaid deserves further consideration when the existing treatment guidelines for OA of the knee are updated.

PMID: 16511925

Rating: 1b

Townsend CO, Bruce BK, Hooten WM, Rome JD. The role of mental health professionals in multidisciplinary pain rehabilitation programs. *J Clin Psychol*. 2006 Aug 25; [Epub ahead of print]

This article discusses the biopsychosocial approach to pain treatment.

PMID: 16937355

Rating: 5b

Townsend CO, Kerkvliet JL, Bruce BK, Rome JD, Hooten WM, Luedtke CA, Hodgson JE. A longitudinal study of the efficacy of a comprehensive pain rehabilitation program with opioid withdrawal: comparison of treatment outcomes based on opioid use status at admission. *Pain*. 2008;140:177-89.

Patients with longstanding CPRP on chronic opioid therapy, who choose to participate in interdisciplinary rehabilitation that incorporates opioid withdrawal, can experience significant and sustained improvement in pain severity and functioning.

PMID: 18804915

Rating: 3b

Tracz MJ, Sideras K, Bolona ER, Haddad RM, Kennedy CC, Uraga MV, Caples SM, Erwin PJ, Montori VM. Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. *J Clin Endocrinol Metab*. 2006;91:2011-6.

Intramuscular testosterone moderately increased lumbar bone density in men; the results on femoral neck bone density are inconclusive. Without bone fracture data, the available trials offer weak and indirect inferences about the clinical efficacy of testosterone on osteoporosis prevention and treatment in men.

PMID: 16720668

Rating: 1a

Tran de QH, Duong S, Bertini P, Finlayson RJ. Treatment of complex regional pain syndrome: a review of the evidence. *Can J Anaesth*. 2010 Feb;57(2):149-66. doi: 10.1007/s12630-009-9237-0.

PMID: 20054678

Rating: 1c

Trevino ME. Grasso AR. ALO-KNT-301: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Efficacy Study of Morphine Sulfate Plus Naltrexone Hydrochloride Extended-Release Capsules in Subjects with Moderate to Severe Chronic Pain Due to Osteoarthritis of theHip or Knee. Aug 13, 2009

The mean change in the weekly diary BPI average pain score from randomization baseline to the end of study was statistically significantly superior for those treated with Embeda compared to the placebo group.

Rating: 2b

Tulder MW van, Malmivaara A, Esmail R, Koes BW. Exercise therapy for low back pain (Cochrane Review). In: *The Cochrane Library,* Issue 2, 2002. Oxford: Update Software.

Conclusions: The evidence summarised in this systematic review does not indicate that specific exercises are effective for the treatment of acute low back pain. Exercises may be helpful for chronic low back pain patients to increase return to normal daily activities and work.

Publication Type: Meta-Analysis

Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain*. 2008;24:497-508.

Strong predictors include a personal history of illicit drug and alcohol abuse.

PMID: 18574359

Rating: 1b

Turner MK, Hooten WM, Schmidt JE, Kerkvliet JL, Townsend CO, Bruce BK. Prevalence and clinical correlates of vitamin D inadequacy among patients with chronic pain. *Pain Med*. 2008 Nov;9(8):979-84.

The prevalence and clinical correlates identified in this pilot study provide the basis for the assertion that vitamin D inadequacy may represent an under-recognized source of nociception and impaired neuromuscular functioning among patients with chronic pain.

PMID: 18346069

Rating: 3a

Turturro MA, Paris PM, Larkin GL. Tramadol versus hydrocodone-acetaminophen in acute musculoskeletal pain: a randomized, double-blind clinical trial. *Ann Emerg Med.* 1998 Aug;32(2):139-43.

Tramadol provides inferior analgesia to hydrocodone-acetaminophen in ED patients with acute musculoskeletal pain.

PMID: 9701294

Rating: 2b

Tutak U, Doleys DM. Intrathecal infusion systems for treatment of chronic low back and leg pain of noncancer origin. *South Med J.* 1996 Mar;89(3):295-300.

These data support chronic spinal opiate therapy as an option for safe and long-term management of noncancer pain.

PMID: 8604459

Rating: 2c

Uher EM, Vacariu G, Schneider B, Fialka V. Comparison of manual lymph drainage with physical therapy in complex regional pain syndrome, type I. A comparative randomized controlled therapy study. *Wien Klin Wochenschr*. 2000 Feb 11;112(3):133-7.

The results 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.

PMID: 10729965

Rating: 2c

Ung H, Brown JE, Johnson KA, Younger J, Hush J, Mackey S. Multivariate Classification of Structural MRI Data Detects Chronic Low Back Pain. *Cereb Cortex*. 2012 Dec 17.

Our findings suggest that cLBP is characterized by a pattern of GM changes that can have discriminative power and reflect relevant pathological brain morphology.

PMID: 23246778

Rating: 3b

United Health Care. Technology Assessment: Intrathecal Pump for Chronic Nonmalignant Pain. Number 2005T0060C, Approved By Medical Technology Assessment Committee 11/17/2005.

An implantable infusion pump is covered when used to administer opioid drugs (e.g., morphine) intrathecally or epidurally for treatment of severe chronic intractable pain of malignant or nonmalignant origin in patients who have a life expectancy of at least 3 months, and who have proven unresponsive to less invasive medical.

Rating: 6b

van der Plas AA, van Rijn MA, Marinus J, Putter H, van Hilten JJ. Efficacy of intrathecal baclofen on different pain qualities in complex regional pain syndrome. *Anesth Analg*. 2013;116:211-5.

PMID: 23223108

Rating: 5c

van Eijs F, Stanton-Hicks M, Van Zundert J, Faber CG, Lubenow TR, Mekhail N, van Kleef M, Huygen F. Evidence-based interventional pain medicine according to clinical diagnoses. 16. Complex regional pain syndrome. *Pain Pract*. 2011;11:70-87.

PMID: 20807353

Rating: 5b

van Eijs F, Geurts J, van Kleef M, Faber CG, Perez RS, Kessels AG, Van Zundert J. Predictors of pain relieving response to sympathetic blockade in complex regional pain syndrome type 1. *Anesthesiology*. 2012;116:113-21.

PMID: 22143169

Rating: 4b

van Geen JW, Edelaar MJ, Janssen M, van Eijk JT. The long-term effect of multidisciplinary back training: a systematic review. *Spine*. 2007;32:249-55

In the long-term, multidisciplinary back training has a positive effect on work participation in patients with nonspecific chronic low back pain.

PMID: 17224822

Rating: 1b

van Rijn MA, Munts AG, Marinus J, Voormolen JH, de Boer KS, Teepe-Twiss IM, van Dasselaar NT, Delhaas EM, van Hilten JJ. Intrathecal baclofen for dystonia of complex regional pain syndrome*. Pain*. 2009;143:41-7.

PMID: 19232828

Rating: 4c

van Tulder M, Koes B, Bouter L. Conservative Treatment of Acute and Chronic Nonspecific Low Back Pain: A Systematic Review of Randomized Controlled Trials of the Most Common Interventions. *Spine* 1997; 22(18):2128-2156. (Includes Letter to the Editor and Response in *Spine* 1998; 23(11): 1288-1291, and Table A: Content of 12 Multidisciplinary Interventions for the Treatment of Chronic Low Back Pain tested in 10 Randomised Controlled Trials.

The quality of the design, execution, and reporting of randomized controlled trials should be improved, to establish strong evidence for the effectiveness of the various therapeutic interventions for acute and chronic low back pain.

Publication Type: Meta-Analysis

PMID: 9322325

van Tulder MW, Scholten RJ, Koes BW, Deyo RA, Nonsteroidal anti-inflammatory drugs for low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group, *Spine*. 2000 Oct 1;25(19):2501-13.

The evidence from the 51 trials included in this review suggests that nonsteroidal anti-inflammatory drugs are effective for short-term symptomatic relief in patients with acute low back pain. Furthermore, there does not seem to be a specific type of nonsteroidal anti-inflammatory drug that is clearly more effective than others.

PMID: 11013503

Rating: 1a

van Tulder MW, Koes B, Malmivaara A. Outcome of non-invasive treatment modalities on back pain: an evidence-based review. *Eur Spine J.* 2006 Jan;15 Suppl 1:S64-81.

Several treatments are also effective for short-term improvement of function in chronic LBP, namely COX2 inhibitors, back schools, progressive relaxation, exercise therapy, and multidisciplinary treatment.

PMID: 16320031

Rating: 1b

Varas-Lorenzo C, Riera-Guardia N, Calingaert B, Castellsague J, Pariente A, Scotti L, Sturkenboom M, Perez-Gutthann S. Stroke risk and NSAIDs: a systematic review of observational studies. *Pharmacoepidemiol Drug Saf*. 2011 Oct 3. doi: 10.1002/pds.2227. [Epub ahead of print]

CONCLUSION: This meta-analysis supports an increased risk of ischemic stroke with the current use of rofecoxib and diclofenac.

PMID: 21971833

Rating: 1b

Varrassi G, Paladini A, Marinangeli F, Racz G. Neural modulation by blocks and infusions. *Pain Pract*. 2006;6:34-8.

The most common indication for nerve blocks, especially sympathetic blockade, is complex regional pain syndrome, in which success rates of up to 38% have been achieved, depending on the type of the block used.

PMID: 17309707

Rating: 5c

Veldhuizen JW, Verstappen FT, Vroemen JP, Kuipers H, Greep JM. Functional and morphological adaptations following four weeks of knee immobilization. *Int J Sports Med*. 1993;14:283-7.

PMID: 8365837

Rating: 3c

Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet.* 1993;342:1012-6.

PMID: 8105263

Rating: 3c

Verdugo RJ, Ochoa JL. Abnormal movements in complex regional pain syndrome: assessment of their nature. *Muscle Nerve*. 2000;23:198-205.

PMID: 10639611

Rating: 4b

Vlaeyen JW, Haazen IW, Schuerman JA, Kole-Snijders AM, van Eek H. Behavioural rehabilitation of chronic low back pain: comparison of an operant treatment, an operant-cognitive treatment and an operant-respondent treatment. *Br J Clin Psychol*. 1995 Feb;34 (Pt 1):95-118.

In general, the results suggest that behavioural rehabilitation programmes for chronic low back pain are effective and that the effects of an operant treatment are magnified when self-control techniques are added.

PMID: 7757046

Rating: 2c

Voerman GE, Vollenbroek-Hutten MM, Hermens HJ. Changes in pain, disability, and muscle activation patterns in chronic whiplash patients after ambulant myofeedback training. *Clin J Pain.* 2006 Sep;22(7):656-63.

Four weeks of ambulant training may be beneficial in reducing pain and disability levels and normalizing muscle activation patterns in chronic WAD patients. A randomized-controlled study is recommended to further explore the effects of myofeedback training.

PMID: 16926582

Rating: 4c

Volkow ND, Fowler JS, Logan J, Alexoff D, Zhu W, Telang F, Wang GJ, Jayne M, Hooker JM, Wong C, Hubbard B, Carter P, Warner D, King P, Shea C, Xu Y, Muench L, Apelskog-Torres K. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. *JAMA*. 2009 Mar 18;301(11):1148-54.

Because drugs that increase dopamine in the nucleus accumbens have the potential for abuse, and considering the increasing use of modafinil, these results highlight the need for heightened awareness for potential abuse of and dependence on modafinil in vulnerable populations.

PMID: 19293415

Rating: 3c

Voshaar RC, Couvée JE, van Balkom AJ, Mulder PG, Zitman FG. Strategies for discontinuing long-term benzodiazepine use: meta-analysis. *Br J Psychiatry*. 2006 ;189:213-20.

PMID: 16946355

Rating: 1c

Vuilleumier PH, Stamer UM, Landau R. Pharmacogenomic considerations in opioid analgesia. *Pharmgenomics Pers Med.* 2012;5:73-87. doi: 10.2147/PGPM.S23422.

PMID: 23226064

Rating: 5b

Waara-Wolleat KL, Hildebrand KR, Stewart GR. A review of intrathecal fentanyl and sufentanil for the treatment of chronic pain. *Pain Med*. 2006;7:251-9.

College of Pharmacy, University of Minnesota, Minnesota 55120, USA. waar0002@umn.edu

Few clinical reports on the use of intrathecal sufentanil or fentanyl for chronic pain are available.

PMID: 16712626

Rating: 5b

Wafford KA, Ebert B. Emerging anti-insomnia drugs: tackling sleeplessness and the quality of wake time. *Nat Rev Drug Discov*. 2008;7:530-40. Epub 2008 May 23.

Eli Lilly UK, Erl Wood Manor, Windlesham, Surrey GU20 6PH, UK.

Here, we review the current understanding of how hypnotic drugs act, and discuss how new, more effective drugs and treatment strategies for insomnia might be achieved by taking into consideration the daytime consequences of disrupted sleep.

Rating: 5c

Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med*. 2013 Apr 11;368(15):1388-97. doi: 10.1056/NEJMoa1204471.

PMID: 23574118

Rating: 3b

Waknine Y. Duloxetine HCl (Cymbalta) Approved for Management of Fibromyalgia. Medscape, LLC. Release Date: June 19, 2008.

Treatment of fibromyalgia with duloxetine should be initiated at 30 mg/day for 1 week and then uptitrated to the recommended 60-mg dose.

Rating: 5b

Walach H, Guthlin C, Konig M. Efficacy of massage therapy in chronic pain: a pragmatic randomized trial. J Altern Complement Med. 2003 Dec;9(6):837-46.

Despite its limitation resulting from problems with numbers and randomization this study shows that massage can be at least as effective as SMC in chronic pain syndromes. Relative changes are equal, but tend to last longer and to generalize more into psychologic domains.

PMID: 14736355

Rating: 2c

Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, Gouaux B, Abramson I. Dose-dependent Effects of Smoked Cannabis on Capsaicin-induced Pain and Hyperalgesia in Healthy Volunteers. *Anesthesiology.* 107(5):785-796, November 2007.

This study suggests that there is a window of modest analgesia for smoked cannabis, with lower doses decreasing pain and higher doses increasing pain.

Rating: 2c

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 P, Barber J, Clayton W, Currell R, Fleming K, Garner P, Haines A, Harrison R, Jacklin P, Jarrett C, Jayasuriya R, Lewis L, Parker S, Roberts J, Thompson S, Wainwright P. Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations. *Health Technol Assess*. 2004 Dec;8(50):1-106, iii-iv.

Department of Primary Care and Population Sciences, Royal Free and University College Medical School, London, UK.

OBJECTIVES: To test the hypotheses that virtual outreach would reduce offers of hospital follow-up appointments and reduce numbers of medical interventions and investigations, reduce numbers of contacts with the health care system, have a positive impact on patient satisfaction and enablement, and lead to improvements in patient health status. RESULTS: Patients in the virtual outreach group were more likely to be offered a follow-up appointment. Significant differences in effects were observed between the two sites and across different specialities. Patient satisfaction was greater after a virtual outreach consultation than after a standard outpatient consultation, with no heterogeneity between specialities or sites. CONCLUSIONS: Virtual outreach consultations result in significantly higher levels of patient satisfaction than standard outpatient appointments and lead to substantial reductions in numbers of tests and investigations, but they are variably associated with increased rates of offer of follow-up according to speciality and site.

PMID: 15546515

Rating: 2a

Walsh JK, Krystal AD, Amato DA, Rubens R, Caron J, Wessel TC, Schaefer K, Roach J, Wallenstein G, Roth T. Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations*. Sleep*. 2007;30:959-68.

CONCLUSIONS: This is the first placebo-controlled investigation to demonstrate that long-term nightly pharmacologic treatment of primary insomnia with any hypnotic enhanced quality of life, reduced work limitations, and reduced global insomnia severity, in addition to improving patient-reported sleep variables.

Rating: 2b

Wang C, Schmid CH, Rones R, Kalish R, Yinh J, Goldenberg DL, Lee Y, McAlindon T. A Randomized Trial of Tai Chi for Fibromyalgia. *N Engl J Med* 2010; 363:743-754, August 19, 2010

Results: Of the 66 randomly assigned patients, the 33 in the tai chi group had clinically important improvements in the FIQ total score and quality of life. Conclusions: Tai chi may be a useful treatment for fibromyalgia and merits long-term study in larger study populations.

Rating: 2b

Washington State Department of Labor and Industries, *Technology Assessment of the Dynatron STS*, Office of the Medical Director, 4/30/02

Insufficient evidence exists to determine Dynatron STS' effectiveness in the treatment of chronic pain.

Rating: 7b

Washington State Department of Labor and Industries. Guidelines for outpatient prescription of oral opioids for injured workers with chronic, noncancer pain. Olympia (WA): Washington State Department of Labor and Industries; 2002 Aug.

Rating: 7a

Washington State Department of Labor and Industries. Antiepileptic drugs guideline for chronic pain. *Provider Bull* 2005 Aug;(PB 05-10):1-3.

Currently, there is lack of evidence to demonstrate that antiepileptic drugs (AEDs) significantly reduce the level of acute pain, myofascial pain, low back pain, or other sources of somatic pain. Gabapentin, along with older antiepileptic drugs, may be used as a first line therapy in the treatment of chronic neuropathic pain. There is no scientific evidence that antiepileptic drugs are effective in treating acute pain, somatic pain from strains or sprains, or myofascial pain.

Rating: 7a

Washington State Department of Labor and Industries. Complex regional pain syndrome (CRPS). Olympia (WA): Washington State Department of Labor and Industries; 2002 Aug.

B. The term "complex regional pain syndrome" was introduced to replace the term "reflex sympathetic dystrophy." CRPS Type I used to be called reflex sympathetic dystrophy. CRPS Type II used to be called causalgia. The central difference between Type I and Type II is that, by definition, Type II occurs following a known peripheral nerve injury, whereas Type I occurs in the absence of any known nerve injury**.**

Table 1. Labor and Industries Criteria Number 13. Chronic Regional Pain Syndrome (CRPS) Conservative Treatment Guideline

Examination Findings And Diagnostic Test Results	Conservative Care
At least **four** of the following **must be present** in order for a diagnosis of CRPS to be made. ***Examination Findings*** 1. Temperature/color change 2. Edema 3. Trophic skin, hair, nail growth abnormalities 4. Impaired motor function 5. Hyperpathia/allodynia 6. Sudomotor changes ***Diagnostic Test Results*** 7. Three phase bone scan that is abnormal in pattern characteristics for CRPS. This test is not needed if 4 or more of the above examination findings are present.	Early aggressive care is encouraged. Emphasis should be on improved functioning of the symptomatic limb. ***First Six Weeks Of Care:*** • Sympathetic blocks, maximum of **five**. Each block should be followed immediately by physical/occupational therapy. • Physical/occupational therapy should be focused on increasing functional level (see Table 2). • Other treatment (e.g., medication at MD's discretion) as long as it promotes improved function. ***After The 1st Six Weeks Of Care:*** • Strongly consider psychiatric or psychological consultation if disability has extended beyond 3 months • Continued physical/occupational therapy based on documented progress towards goals established during first 6 weeks (referenced above). • Sympathetic blocks only if response to previous blocks has been positive, maximum of 3** every six weeks for a maximum of 12 weeks.
Surgical Interventions (Sympathetectomy) For Treatment Of This Condition Is Not Covered	****A maximum of 11 blocks can be delivered over the total 18 week period**

Rating: 7a

Washington State Health Care Authority. Health Technology Clinical Committee Findings and Coverage Decision, Implantable Drug Delivery System. Number and Coverage Topic 20080815A, Approved By Health Technology Clinical Committee 11/14/2008.

Rating: 7a

Washington State Health Care Authority. HTA final report implantable infusion pumps for chronic noncancer pain. ECRI Institute, July 18, 2008.

Wasner G, Schattschneider J, Baron R. Skin temperature side differences--a diagnostic tool for CRPS? *Pain*. 2002 Jul;98(1-2):19-26.

Skin temperature differences in the distal limbs are capable of reliably distinguishing CRPS I from other extremity pain syndromes with high sensitivity and specificity.

PMID: 12098613

Wasner G. Vasomotor disturbances in complex regional pain syndrome--a review. *Pain Med*. 2010;11:1267-73.

PMID: 20704675

Rating: 5c

Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. *Brain.* 2001;124:587-99.

PMID: 11222458

Rating: 4b

Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW, Harris SC. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. *JAMA*. 2006 Jul 5;296(1):87-93.

Should add caution about daily dose of acetaminophen and liver disease if > 4 g/day or in combination with other NSAID.

PMID: 16820551

Rating: 2b

Webster LR, Cochella S, Dasgupta N, Fakata KL, Fine PG, Fishman SM, Grey T, Johnson EM, Lee LK, Passik SD, Peppin J, Porucznik CA, Ray A, Schnoll SH, Stieg RL, Wakeland W. An analysis of the root causes for opioid-related overdose deaths in the United States. Pain Med. 2011;12:S26-35.

Although methadone represented less than 5% of opioid prescriptions dispensed, one third of opioid-related deaths nationwide implicated methadone.

PMID: 21668754

Rating: 5b

Weiss RD, Potter JS, Fiellin DA, Byrne M, Connery HS, Dickinson W, Gardin J, Griffin ML, Gourevitch MN, Haller DL, Hasson AL, Huang Z, Jacobs P, Kosinski AS, Lindblad R, McCance-Katz EF, Provost SE, Selzer J, Somoza EC, Sonne SC, Ling W. Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence: A 2-Phase Randomized Controlled Trial. *Arch Gen Psychiatry.* 2011 Nov 7. [Epub ahead of print]

Prescription opioid-dependent patients are most likely to reduce opioid use during buprenorphine-naloxone treatment.

PMID: 22065255

Rating: 2a

Wepner F, Scheuer R, Schuetz-Wieser B, Machacek P, Pieler-Bruha E, Cross HS, Hahne J, Friedrich M. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. *Pain.* 2014 Feb;155(2):261-8. doi: 10.1016/j.pain.2013.10.002.

PMID: 24438771

Rating: 2b

Wenham CY, Conaghan PG. Optimising pain control in osteoarthritis. *Practitioner*. 2010;254:23-6, 2-3.

Paracetamol and topical NSAIDs should be tried before oral NSAIDs. Topical NSAIDs are effective in the short-term and are not associated with systemic toxicity. Oral NSAIDs should be used at the lowest effective dose for the shortest possible time.

PMID: 21306035

Rating: 5a

Wermeling DP. Ziconotide, an intrathecally administered N-type calcium channel antagonist for the treatment of chronic pain. *Pharmacotherapy.* 2005 Aug;25(8):1084-94.

Therefore, patients with psychiatric symptoms are not candidates for this drug.

PMID: 16207099

Rating: 5a

Wermeling DP. Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access. Ther Adv Drug Saf. 2015;6:20-31.

PMID: 25642320

Rating: 5c

Weschules DJ, Bain KT, Richeimer S. Actual and potential drug interactions associated with methadone. *Pain Med*. 2008;9:315-44.

Genetic variability may play a role in the pharmacokinetics and pharmacodynamics of many medications, including methadone.

PMID: 18386306

Rating: 1a

Wheeler AH, Goolkasian P, Gretz SS. A Randomized, Double-Blind, Prospective Pilot Study of Botulinum Toxin Injection for Refractory, Unilateral, Cervicothroacic, Paraspinal, Myofascial Pain Syndrome. *Spine* 1998;23:1662-7.

First injections of Botox were not significantly different from saline injection, and not clearly better than would be expected from dry needling. Second injection did produce noticeable group difference, with advantage for those who had received Botox at first injection, but difference not significant and meaning unclear

Publication Type: RCT, 32

PMID: 11731062

Rating: 2b

White JA, Tao X, Artuso RD, Bilinski C, Rademacher J, Bernacki EJ. Effect of physician-dispensed medication on workers' compensation claim outcomes in the state of Illinois. J Occup Environ Med. 2014 May;56(5):459-64. doi: 10.1097/JOM.0000000000000145.

OBJECTIVE: To evaluate differences between physician-dispensed and non-physician-dispensed medication with regard to lost time, prescription volume, and pharmaceutical, medical, indemnity costs in the Illinois workers' compensation system.

METHODS: They studied a sample of 6824 workers' compensation indemnity claims that were opened and closed between January 1, 2007, and December 31, 2012, by Accident Fund Holdings in the State of Illinois.

RESULTS: The number of prescriptions per claim and pharmaceutical, medical, and indemnity costs, as well as time out from work, were significantly higher in claims where a pharmaceutical was dispensed by the physician within 90 days of injury than in claims where physician dispensing did not occur. These differences persisted controlling for age, sex, attorney involvement, and injury complexity.

CONCLUSION: Physician dispensing is associated with higher costs and more lost time than pharmacy-dispensed medications in workers' compensation claims.

PMID: 24806556

Rating: 4a

Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. *Cochrane Database Syst Rev.* 2005 Jul 20;(3):CD001133.

Although anticonvulsants are used widely in chronic pain surprisingly few trials show analgesic effectiveness. Only one study considered cancer pain. There is no evidence that anticonvulsants are effective for acute pain. In chronic pain syndromes other than trigeminal neuralgia, anticonvulsants should be withheld until other interventions have been tried. While gabapentin is increasingly being used for neuropathic pain the evidence would suggest that it is not superior to carbamazepine.

PMID: 16034857

Rating: 1a

Conclusion: Currently, there is lack of evidence to demonstrate that AEDs significantly reduce the level of acute pain, myofascial pain, low back pain, or other sources of somatic pain.(2)
(2) Cochrane Review. Anticonvulsant drugs for acute and chronic pain. The Cochrane Database of Systematic Reviews, 2005; 1.

Wiffen PJ, McQuay HJ, Edwards JE, Moore RA. Gabapentin for acute and chronic pain. *Cochrane Database Syst Rev*. 2005 Jul 20;(3):CD005452.

There is evidence to show that gabapentin is effective in neuropathic pain. There is limited evidence to show that gabapentin is ineffective in acute pain.

PMID: 16034978

Rating: 1a

Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):CD006044.

Given the availability of more effective treatments including anticonvulsants and antidepressant medicines, lamotrigine does not have a significant place in therapy at present. The limited evidence currently available suggests that lamotrigine is unlikely to be of benefit for the treatment of neuropathic pain.

PMID: 17443611

Rating: 1b

Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice ASC, Lunn MPT, Hamunen K, Haanpaa M, Kalso EA. Antiepileptic drugs for neuropathic pain and fibromyalgia – an overview of Cochrane reviews (Review). Cochrane Database Syst Rev. 2013 Nov 11;(11):CD010567.

PMID: 24217986

Rating: 1a

Wild JE, Grond S, Kuperwasser B, Gilbert J, McCann B, Lange B, Steup A, Häufel T, Etropolski MS, Rauschkolb C, Lange R. Long-term Safety and Tolerability of Tapentadol Extended Release for the Management of Chronic Low Back Pain or Osteoarthritis Pain. *Pain Pract.* 2010 Jun 29. [Epub ahead of print]

Results: A total of 1,117 patients received at least 1 dose of study drug. Gastrointestinal treatment-emergent adverse events led to discontinuation in 8.6% versus 21.5% of patients.

PMID: 20602712

Rating: 2b

Note: Tapentadol ER is not yet approved by the FDA.

Wilhelmsen M, Amirian I, Reiter RJ, Rosenberg J, Gögenur I. Analgesic effects of melatonin: a review of current evidence from experimental and clinical studies. *J Pineal Res*. 2011 Oct;51(3):270-7. doi: 10.1111/j.1600-079X.2011.00895.x.

In clinical studies, melatonin has been shown to have analgesic benefits in patients with chronic pain.

PMID: 21615490

Rating: 5b

Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain.* 2008 Jun;9(6):506-21. Epub 2008 Apr 10.

This study adds to a growing body of evidence that cannabis may be effective at ameliorating neuropathic pain, and may be an alternative for patients who do not respond to, or cannot tolerate, other drugs. However, the use of marijuana as medicine may be limited by its method of administration (smoking) and modest acute cognitive effects, particularly at higher doses.

PMID: 18403272

Rating: 2c

Winkelmuller M, Winkelmuller W. Long-term effects of continuous intrathecal opioid treatment in chronic pain of nonmalignant etiology. *J Neurosurg*. 1996 Sep;85(3):458-67.

Ninety-two percent of the patients were satisfied with the therapy and 81% reported an improvement in their quality of life.

PMID: 8751633

Rating: 3b

Wise J. True risks of paracetamol may be underestimated, say researchers. *BMJ.* 2015 Mar 2;350:h1186. doi: 10.1136/bmj.h1186.

PMID: 25736341

Rating: 1b

Witt CM, Schützler L, Lüdtke R, Wegscheider K, Willich SN. Patient Characteristics and Variation in Treatment Outcomes: Which Patients Benefit Most From Acupuncture for Chronic Pain? *Clin J Pain.* 2011 Feb 11. [Epub ahead of print]

Patients' characteristics that enlarged the acupuncture effect were being female, living in a multi-person household, failure of other therapies before the study, and former positive acupuncture experience.

PMID: 21317771

Rating: 1b

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. Arthritis Rheum 1990;33:160---72.

American College of Rheumatology, 1990 criteria for the classification of Fibromyalgia
1. History of widespread pain.
2. Pain in 11 of 18 tender point sites on digital palpation.
Digital palpation should be performed with an approximate force of 4 kg.
For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender is not to be considered "painful."
* For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

Rating: 6b

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken).* 2010 May;62(5):600-10.

RESULTS: The most important diagnostic variables were WPI and categorical scales for cognitive symptoms, unrefreshed sleep, fatigue, and number of somatic symptoms.

PMID: 20461783

Rating: 4b

Wolfe GI, Trivedi JR. Painful peripheral neuropathy and its nonsurgical treatment. *Muscle Nerve*. 2004;30:3-19.

Antidepressants and anticonvulsants are the two pharmacological classes most widely studied and represent first-line agents in the management of neuropathic pain.

PMID: 15221874

Rating: 5b

Wong MC, Chung JW, Wong TK. Effects of treatments for symptoms of painful diabetic neuropathy: systematic review. *BMJ.* 2007;335:87. Epub 2007 Jun 11.

Oral tricyclic antidepressants and traditional anticonvulsants are better for short-term pain relief than newer generation anticonvulsants. Evidence of the long-term effects of oral antidepressants and anticonvulsants is still lacking.

PMID: 17562735

Rating: 1b

Wright TM, Cluver JS, Myrick H. Management of intoxication and withdrawal: General principles. In Reis RK, Fiellin DA, Miller SC, Saitz R. eds. Principles of Addiction Medicine, 4th edition. Lippincott Williams & Wilkins, 2009.

An overview of the natural history and variations found with withdrawal from substances known for abuse. It is noted that all therapies should be tailored to the patient's needs and adjusted to response to treatment.

Rating: 9a

Wüppenhorst N, Maier C, Frettlöh J, Pennekamp W, Nicolas V. Sensitivity and specificity of 3-phase bone scintigraphy in the diagnosis of complex regional pain syndrome of the upper extremity. *Clin J Pain*. 2010;26:182-9.

PMID: 20173431

Rating: 4b

Wynn BO. Use of Compound Drugs, Medical Foods, and Co-Packs in California's Workers' Compensation Program, An Overview of the Issues. WR-828-CHSWC. RAND Institute for Civil Justice. Prepared for the Commission on Health, Safety and Workers' Compensation. January 2011.

The purpose of this paper is to explore the issues surrounding the use of compound drugs, co-packs and medical foods under the California workers' compensation (WC) program and to assess whether policy changes are needed to promote medically appropriate and efficient use of these products.

Rating: 5a

Yaksi A, Ozgönenel L, Ozgönenel B. The efficiency of gabapentin therapy in patients with lumbar spinal stenosis. *Spine*. 2007 Apr 20;32(9):939-42.

Gabapentin treatment resulted in an increase in the walking distance better.

PMID: 17450066

Rating: 2c

Yentur EA, Okcu G, Yegul I. The role of trigger point therapy in knee osteoarthritis*. Pain Clinic* 2003;15:385-90.

Physical activity results improved significantly for the combined group vs. the group with the intra-articular injection (improvement in squatting and walking only).

Rating: 2c

Yokoyama M, Sun X, Oku S, Taga N, Sato K, Mizobuchi S, Takahashi T, Morita K. Comparison of percutaneous electrical nerve stimulation with transcutaneous electrical nerve stimulation for long-term pain relief in patients with chronic low back pain. *Anesth Analg.* 2004 Jun;98(6):1552-6, table of contents.

Results indicate that although PENS is effective for chronic LBP, treatments need to be continued to sustain analgesia.

PMID: 15155304

Rating: 2b

Note: Not a “curative” treatment.

Yoshida GM, Nelson RW, Capen DA, Nagelberg S, Thomas JC, Rimoldi RL, Haye W. Evaluation of continuous intraspinal narcotic analgesia for chronic pain from benign causes. *Am J Orthop.* 1996 Oct;25(10):693-4.

Overall, only 4 patients had objective evidence of benefit from INA, for a success rate of 25%. Results of this review suggest INA should not be used for the long-term management of chronic pain from nonmalignant causes.

PMID: 8922167

Rating: 4b

Yousefi-Nooraie R, Schonstein E, Heidari K, Rashidian A, Akbari-Kamrani M, Irani S, Shakiba B, Mortaz Hejri S, Mortaz Hejri S, Jonaidi A. Low level laser therapy for nonspecific low-back pain. *Cochrane Database Syst Rev.* 2007 Apr 18;(2):CD005107.

There is a need for further methodologically rigorous RCTs to evaluate the effects of LLLT compared to other treatments, different lengths of treatment, different wavelengths and different dosages.

PMID: 17443572

Rating: 1b

Yung Chung O, Bruehl SP. Complex Regional Pain Syndrome. *Curr Treat Options Neurol*. 2003 Nov;5(6):499-511.

Sympathetic nerve blocks should be performed at least once to assess if sympathetically maintained pain is present. Pain relief, however it is achieved and however temporary it is, is intended to facilitate participation in functional therapies to normalize use and to improve motion, strength, and dexterity.

PMID: 14516527

Rating: 5a

Zambito A, Bianchini D, Gatti D, Viapiana O, Rossini M, Adami S. Interferential and horizontal therapies in chronic low back pain: a randomized, double blind, clinical study. *Clin Exp Rheumatol.* 2006 Sep-Oct;24(5):534-9.

This randomized double-blind controlled study provides the first evidence that IFT and HT therapy are significantly effective in alleviating both pain and disability in patients with CLBP. The placebo effect is remarkable at the beginning of the treatment but it tends to vanish within a couple of weeks.

PMID: 17181922

Rating: 2b

Zambito A, Bianchini D, Gatti D, Rossini M, Adami S, Viapiana O. Interferential and horizontal therapies in chronic low back pain due to multiple vertebral fractures: a randomized, double blind, clinical study. *Osteoporos Int.* 2007 Nov;18(11):1541-5. Epub 2007 Jul 4.

This randomized double-blind controlled study provides the first evidence that IFT and HT therapy are significantly effective in alleviating both pain and disability in patients with CBPMF.

PMID: 17609842

Rating: 2b

Zammit G, Erman M, Wang-Weigand S, Sainati S, Zhang J, Roth T. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J Clin Sleep Med.* 2007;3:495-504.

Ramelteon reduced LPS over 5 weeks of treatment in subjects with chronic insomnia, with no clinically meaningful sleep architecture alterations, next-morning residual pharmacologic effects, and no evidence of rebound insomnia or withdrawal.

Rating: 2c

Zaremba PD, Białek M, Błaszczyk B, Cioczek P, Czuczwar SJ. Non-epilepsy uses of antiepilepsy drugs. *Pharmacol Rep.* 2006;58:1-12.

Both conventional and newer AEDs may be used in patients suffering from neuropathic pain, migraine, essential tremor, spasticity, restless legs syndrome and a number of psychiatric disorders (f.e. bipolar disease or schizophrenia).

PMID: 16531624

Review: 5b

Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16:137-62.

PMID: 18279766

Rating: 6a

Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, Dinçer F, Dziedzic K, Häuselmann HJ, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Maheu E, Martín-Mola E, Pavelka K, Punzi L, Reiter S, Sautner J, Smolen J, Verbruggen G, Zimmermann-Górska I. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2007;66:377-88.

CONCLUSION: Eleven key recommendations for treatment of hand OA were developed.

PMID: 17046965

Rating: 6a

The recommendation made was that local treatments were preferred over systemic treatments, especially for mild to moderate pain and when only a few joints were affected. Topical NSAIDs and capsaicin were considered effective and safe treatments for hand OA.

Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage*. 2010;18:476-99.

Among pharmacological therapies, the cumulative evidence for the benefits and harms of oral and topical non-steroidal anti-inflammatory drugs, diacerhein and intra-articular (IA) corticosteroid was not greatly changed.

PMID: 20170770

Rating: 6a

Zhang CS, Yang AW, Zhang AL, May BH, Xue CC. Sham control methods used in ear-acupuncture/ear-acupressure randomized controlled trials: a systematic review. *J Altern Complement Med*. 2014 Mar;20(3):147-61. doi: 10.1089/acm.2013.0238.

PMID: 24138333

Rating: 1c

Zuniga JR, Noveck RJ, Schmidt WK, Boesing SE, Hersh EV. Onset of action of diclofenac potassium liquid-filled capsules in dental surgery patients. *Curr Med Res Opin*. 2011 Sep;27(9):1733-9.

These results indicate that DPSGC was efficacious in providing a rapid onset of confirmed perceptible pain relief within 30 minutes of administration in these single dose postoperative dental pain studies.

PMID: 21770716

Rating: 2b

Zwanzger P, Diemer J, Jabs B. Comparison of combined psycho- and pharmacotherapy with monotherapy in anxiety disorders: controversial viewpoints and clinical perspectives. *J Neural Transm.* 2008 Sep 23. [Epub ahead of print]

Anxiety disorders are among the most frequent psychiatric disorders. Experimental evidence supports both psychotherapy as well as pharmacotherapy as effective treatments. We present the results from two recent meta-analyses and discuss implications for clinical practice and further research. We suggest that a research strategy that strives to establish differential indications based on patient characteristics should be preferred over attempts to reach a global judgement of the question, which appears too simplistic given the complexity of the issue.

PMID: 18810307

Rating: 5a

Zyluk A, Puchalski P. Complex regional pain syndrome: observations on diagnosis, treatment and definition of a new subgroup. *J Hand Surg Eur.* Vol. 2013; 38:599-606.

PMID: 23221182

Rating: 5c