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# Evidence-based pain medicine for primary care physicians

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**ABSTRACT**

The last several decades have seen a marked increase in both the recognition and treatment of chronic pain. Unfortunately, patients frequently misunderstand both the nature of pain and the best practices for its treatment. Because primary care physicians treat the majority of chronic pain, they are ideally situated to provide evidence-based pain care. The majority of the medical evidence supports a biopsychosocial model of pain that integrates physical, emotional, social, and cultural variables. The goal of this primer is to assist primary care physicians in their understanding of pain, evaluation of the chronic pain patient, and ability to direct evidence-based care. This article will discuss the role of physical rehabilitation, pain psychology, pharmacotherapy, and procedural interventions in the treatment of chronic pain. Given the current epidemic of drug-related deaths, particular emphasis is placed on the alternatives to opioid therapy. Unfortunately, death is not the only significant complication from opioid therapy, and this article discusses many of the most common side effects. This article provides general guidelines on the most appropriate utilization of opioids with emphasis on the recent Centers for Disease Control and Prevention guidelines, risk stratification, and patient monitoring. Finally, the article concludes with the critical role that a pain medicine specialist can play in the management of patients with chronic pain.

**KEYWORDS** acute pain; chronic pain; opioids; pain interventional procedures; pain medicine; psychological treatment for pain; rehabilitation treatment for pain



During the last several decades, physicians have witnessed an increased emphasis on the assessment and treatment of pain. Unfortunately, for many practitioners there remains a great deal of confusion as to what constitutes appropriate care for the patient with pain. This is due in part to the fact that medical education has not focused on the fundamentals of pain medicine. Fortunately, over the past two decades, the field of pain medicine has evolved into a distinct medical subspecialty with a growing level of sophistication that includes expanded fellowship training programs, board certification, and research programs.[1] These advancements have led to significantly improved treatments for many types of acute and chronic pain syndromes.

The goal of this publication is to review the basic principles of pain medicine and provide primary care providers with a pragmatic and evidence-based approach to optimize assessment and treatment of patients with a variety of painful conditions.

## WHAT IS PAIN?

*Pain* is formally defined as an unpleasant sensory and emotional experience with actual or potential tissue damage or described in terms of such damage.[2] Two important consequences of this definition are that pain (a) is an emotional experience and is therefore influenced by other emotional states and (b) can occur without tissue damage.

Because pain has both somatosensory (physical) and somatoaffective (emotional) components and is processed and interpreted in the context of higher-order cognitive processes, pain assessment must include both a physical and a psychosocial component.[3] For example, a traditional visual analog scale (VAS) is actually a composite score of a complex interaction between physical and psychosocial factors. However, the VAS (0–10 scale) is an inadequate tool to assess complex interactions between physical and psychosocial interactions. Such unidimensional tools assess only the global impact of suffering, not the individual factors impacting the perception of pain and suffering.[4]

Though acute pain has traditionally been considered a reflection of tissue damage, new evidence challenges this notion and unifies the experience of acute pain with chronic pain conditions. The primary differences between acute and chronic pain appear to be that acute pain dissipates as the tissue heals, whereas chronic pain persists beyond the normal healing period (i.e., 3–6 months). It no longer appears that, at some "magic point" in the pain process, psychosocial comorbidities

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begin to emerge. In fact, premorbid psychosocial comorbidities are predictive of the development of chronic pain and perceived disability.[5]

The biopsychosocial model of pain unifies physical and psychosocial aspects of pain and is the best studied and most widely accepted vehicle to integrate different factors important in the experience of pain and suffering. This model includes emotional, cultural, social, religious, financial, existential, and physical factors that interact in a complex, multifactorial way to produce the experience of pain and suffering.[2,6] Suffering relates to the impact of pain on the whole person. It impacts the patient socially, psychologically, financially, and spiritually and can also influence family and personal functioning. In other words, suffering is the inability to cope with adversity.

Biopsychosocial issues are important because they compound conditions, which can distort a patient's perception of pain and disability. Therefore, assessment of pain should include an assessment of the patient's educational background, cultural belief systems, social conditions, and psychological and psychiatric comorbidities in addition to the patient's physical states. Only by addressing the patient's whole person can function be maximally restored and pain and suffering be optimally treated.

## HISTORICAL UNDERTREATMENT OF PAIN

Thirty years ago, there were no standardized tools for pain assessment and little research or recognition given to pain as a symptom, painful disease states, or pain control, even for patients with cancer. There was little or no direct discussion with patients about pain control and often no mention of pain in their medical records. In fact, until the 1970s, health care providers generally did not recognize that patients with cancer suffered significant pain for extended periods of time.

In the mid-1980s, the World Health Organization (WHO), state cancer pain initiatives, and allied groups put forth the seemingly simple recommendation that cancer pain of increasing severity must be aggressively treated with increasingly potent analgesia. This is nothing more than a restatement of the age-old principle of treating any progressing disease with more aggressive therapy until an adequate response is achieved. But when this "WHO stepladder" to cancer pain management was published in 1986, many considered it to be a revolutionary concept.[7]

With the successful implementation of the WHO guidelines, barriers to opioid prescribing were addressed and medicine appeared to make a huge leap forward in the alleviation of pain and suffering. Following the utilization of opioids for cancer pain, many medical societies, patient advocacy groups, pharmaceutical manufacturers, and physicians called for their expanded utilization in chronic noncancer pain. As such, between 1980 and 2000, the use of chronic opioid therapy (COT) for musculoskeletal pain syndromes more than doubled. Furthermore, the US Congress proclaimed 2000 to 2010 to be the "decade of pain management," leading to further research and promulgation in pain medicine and in opioids in particular. It is interesting that the clinical effectiveness of COT remains controversial.[8] However, this increase in COT has been associated with a significant increase in opioid-related side effects and death.

Recognition of chronic pain as a legitimate disease entity has spurred research into numerous treatment options. Conservative therapies such as rehabilitation-based approaches (e.g., exercise physical rehabilitation and physical therapy), as well as treating the psychological aspects of chronic pain (e.g., biofeedback techniques, mindfulness, cognitive restructuring, and adaptive coping strategies), provide excellent evidence-based treatment for many patients. These therapies are often used independently or in conjunction with analgesic medications, nerve blocks, and even implantable devices in the appropriately selected patient.

## SHOULD PAIN BE A VITAL SIGN?

In the 1990s, The Joint Commission, Department of Veterans Affairs, and the American Pain Society adopted pain as "the fifth vital sign."[9] The consideration of pain as a vital sign allows hospital committees to create and ensure a local standard of practice in the recognition and treatment of pain. The Joint Commission has mandated this for hospital and facility accreditation. However, the fifth vital sign, though well intended, is not supported by a deeper understanding of the complex and multifactorial interactions between pain and psychosocial comorbidities.[10,11] Using the VAS as if it represents a vital sign (such as blood pressure) or a laboratory value (such as a glucose level) will often result in suboptimal outcomes, *especially* in the population with chronic pain. Understanding the differences between suffering and pain will improve treatment outcomes.[12] With acute pain, usually a fairly simple algorithm of intravenous analgesics with a transition to oral agents will suffice, whereas with chronic pain, the situation is much more complex.

## OVERVIEW OF TREATMENT STRATEGIES

The effective management of pain is aligned with the basic tenets of good medical care, which begins with a comprehensive assessment. This evaluation should include the following:

- A review of all pertinent previous medical records.
- A detailed history of the pain (which includes information about its etiology, as well as a complete description of the site(s), pattern, intensity, and pathophysiology of the pain—i.e., somatic, visceral, neuropathic—to the extent known).
- Past treatments, consultations, and diagnostic testing, as well as past or present disabilities, mental health disorders, and substance abuse history, including alcohol use disorder, prescription and illicit substance abuse, and nicotine dependency.
- A physical exam including neurological and orthopedic examinations and/or directed exam of the painful site.
- A discussion of expectations and realistic outcomes.

- Finally, the development of a management plan including goals, relevant diagnoses, treatment, and re-evaluation.

A full medical history includes information about the existence of comorbidities, current medications, and a psychosocial evaluation (psychiatric history, patient distress, support systems, history of substance abuse, and patient/family attitudes about pain and its treatment). Clinicians should pay careful attention to new complaints of pain and progressive functional decline. For example, in patients with chronic spine pain, progressive functional decline may indicate progression of comorbid psychosocial issues or further spinal deterioration and impending myelopathy or other neurological compromise. Patients with chronic pain might also present with an acute crisis from new etiologies that should be thoroughly evaluated. In general, the perception of disability is driven by psychosocial comorbidities, whereas functional decline is a result of both physical and psychosocial factors.[13–15]

The goals of pain medicine include improving pain control, improving function, and enhancing coping skills to deal with ongoing pain. The ideal treatment plan for a given patient will depend on the specific clinical situation and will generally involve multidisciplinary treatment. Treatment modalities used to treat chronic pain include physical rehabilitation therapeutics (physical therapy, exercise, massage), psychological pain therapy, pharmacological therapy, interventional procedures (injections, neural blockade, implantable devices), surgical procedures (especially if progressive neurological compromise is present), and complementary and alternative medicine techniques and therapies.[16]

Effective pain management strategies require repeated assessments at regular intervals throughout treatment to monitor the effectiveness of interventions, as well as possible side effects. Successful treatment outcomes are often multimodal and require a multidisciplinary approach for most complex chronic pain syndromes.

## PHYSICAL, COMPLEMENTARY, AND PSYCHOLOGICAL THERAPIES

### Physical medicine therapeutics

Preventing disability and maintaining or improving function are goals of chronic pain management. Along with psychosocial interventions, physical medicine therapeutics and rehabilitation concepts are mainstays of treatment. Therapeutic exercise, education programs, cortically directed sensory–motor rehabilitation strategies, and physical modalities are often utilized by the rehabilitation team. However, in addition to short-term, formalized physical rehabilitation, an ongoing program must be incorporated into the day-to-day activities of a patient with chronic pain. Home exercise and long-term self-management programs, along with ongoing guidance and encouragement, must be incorporated into the treatment plan.

Physical rehabilitation therapeutics to lessen pain symptoms include stretching, strengthening, endurance exercise, thermal modalities, assistive devices, and patient education. These interventions promote soft tissue healing and adaptive neuroplastic changes but, more important, physical medicine and rehabilitation interventions aim to restore function and prevent recurrent injury. These therapeutic options are vital for a comprehensive approach to the treatment of chronic pain.

### Physical modalities

Physical modalities are agents used to produce therapeutic tissue responses. For example, thermal tissue changes via heat or cold improve pain, at least temporarily. Paraffin baths and moist hot packs provide superficial heat. Cold therapy is also used for pain control, because it slows nerve conduction velocity, reduces blood flow through vasoconstriction, and reduces intra-articular temperature.[17] Cold therapy is often effectively used for sports injuries and other acute tissue disruption.

Transcutaneous electrical nerve stimulation is another physical modality commonly used by patients with chronic pain. Despite its widespread use, there remains inconsistent evidence of its effectiveness.[18] Inconclusive findings may be due to inappropriate outcome assessments and inadequate transcutaneous electrical nerve stimulation delivery; therefore, patients must be adequately trained to appropriately self-administer the devices.

### Therapeutic exercise and activity

Though physical modalities may temporarily reduce pain and provide an alternative to pharmacological therapy, they are passive approaches to pain management. It has been shown that active treatments are more effective than passive treatments in general. A therapeutic exercise program for pain can be divided into musculoskeletal flexibility and strength training, along with an aerobic and endurance program. Adherence to a stretching program improves flexibility within 1 to 2 months. Stretching has been found to provide immediate relief for sore muscles after isometric contractions.[19] The use of systematic stretching maneuvers by a physical rehabilitation provider increases functional gains in patients with chronic low back pain.[20,21] Strength training may benefit some fibromyalgia syndrome symptoms.[22] Aerobic fitness and endurance have also been found to be effective in fibromyalgia syndrome. There is evidence that supervised aerobic exercise training has beneficial effects on physical capacity and fibromyalgia symptoms.[22] Decreased neck muscle strength in all directions has been found in women with chronic neck pain, and this should be considered when planning physical rehabilitation programs.[23]

To improve overall function, encouraging active participation in an exercise or activity program should be paramount. To maintain overall health, the *Physical Activity Guidelines for Americans* report recommends 30 minutes daily of physical activity for adults aged 18 to 64, where *physical activity* is defined as any form of exercise or movement of the body that uses energy.[24] It is often difficult for patients with chronic pain to comply with activity or exercise guidelines. However, there is growing evidence that certain activities reduce pain. For example, yoga has been shown to be a cost-effective way to

improve nonspecific low back pain in 6 weeks when recommendations are adhered to.[25] Aquatic aerobic exercise programs have been shown to be effective for the treatment of physical and psychological parameters in female patients with fibromyalgia.[26] There is also some evidence that supports a walking exercise program for chronic musculoskeletal pain.[27]

The preponderance of evidence indicates that physical therapeutics is both a safe and evidence-based option for the treatment of pain. As such, it should be a centerpiece of any pain management plan.

### Complementary modalities

The most recent treatment guidelines from the American College of Physicians (ACP) recommend nonpharmaceutical treatments for acute and chronic low back pain as first-line treatments.[28] Previously considered first-line pharmaceutical agents such as acetaminophen are no more effective than a placebo. Nonsteroidal anti-inflammatory drugs (NSAIDs) have shown moderate quality evidence for small improvement in pain. However, ACP reports that several randomized controlled trials showed no difference in pain relief compared to a placebo.

ACP recommends tai chi, yoga, massage, spinal manipulation, and acupuncture in addition to exercise, psychological therapies including cognitive behavioral therapy and mindfulness-based stress reduction, and multidisciplinary rehabilitation.[28]

### Psychological pain therapy

Psychosocial comorbidities are commonly seen in patients with chronic pain.[19,29–40] They include depression, anxiety, maladaptive personality styles, maladaptive coping mechanisms (fear avoidance, catastrophizing, injustice, disability conviction, inability to accept one's pain, etc.), and negative family dynamics. Cultural factors and personal belief systems may also manifest in maladaptive behaviors that increase pain.

The incidence of depression and anxiety ranges from 40% to 80% in the population with chronic pain.[36] Depression is associated with lowered pain tolerance and decreases a patient's willingness or ability to comply with medical advice. Anxiety interferes with a patient's ability to concentrate and comprehend information. Anxiety may lead to increased muscle tone/spasms, activity avoidance, and pain hypervigilance.[35] Benzodiazepine treatment for comorbid anxiety and/or depression in the patient with chronic pain is not recommended.[41,42]

Hypervigilance and pain-related activity avoidance can lead to anatomical disuse, perception of disability, depression, and low self-esteem. Depression and pain-related anxiety are potent predictors of observable physical performance deficits and increased self-reported functional disability levels.

Fear-avoidance beliefs are strongly related to functional disability in daily living and work. In fact, fear-avoidance issues correlate with functional disability in daily living, to a greater degree than pain intensity.[37,40,43] Because avoidance occurs in anticipation of pain, not just in response to pain, avoidance may easily persist and become dissociated from the actual pain experience. This challenges the notion that lower performance and ability to accomplish tasks of daily living is merely the consequence of pain severity.[34–36]

Personality styles interact with personal belief systems, coping strategies, family dynamics, and cultural expectations to produce a complex reaction to the perception of pain. Comorbid biopsychosocial issues distort the perception of pain and disability, leading to feelings of helplessness, which can be reinforced by family and cultural beliefs. Families that are not supportive can be as counterproductive for the patient as families that enable maladaptive beliefs and behaviors.

Comorbid psychosocial issues are known risk factors for developing chronic pain syndromes after an acute injury and increase the likelihood that a patient will pursue disability benefits because of pain. Comorbid psychosocial issues are also associated with poor coping strategies, aberrant use of controlled substances, and failure to benefit from interventional strategies.[19,37]

Therefore, in order to achieve the best overall patient outcome and the effective control of pain, identification and effective treatment of comorbid biopsychosocial depression, anxiety, fear avoidance, and maladaptive coping strategies are required as an adjuvant strategy to restore physical function. Failure to adequately treat comorbid conditions is likely to compromise the quality and success of chronic pain management. Effective chronic pain management is suffering management combined with functional restoration. Pain treatments are unlikely to produce durable benefits if physicians do not address why the patient is suffering from pain.

The pain psychologist can improve the overall success of chronic pain treatment by providing a thorough evaluation of comorbid depression, anxiety, personality style, coping strategies, pain, and suffering. The psychologist can ally with the patient through the use of motivational interviewing and cognitive-behavioral techniques to help the patient gain insight into his or her maladaptive behaviors and to provide positive reinforcement of his or her adaptive coping skills. Psychotherapy is an evidence-based conservative treatment. However, not all psychologists are created equally. A pain psychologist (or health psychologist, if a pain psychologist is not available) has additional training in medical psychology, understands the chronic pain medical literature, and is comfortable in diagnosing and treating depression, anxiety, maladaptive coping mechanisms, personality disorders, and disability conviction.

### Disability

Disability is the result of a complex interaction between physical, psychosocial, cultural, and educational processes. An in-depth discussion of disability is beyond the scope of this article. However, comorbid psychosocial factors are the strongest predictors of disability from chronic pain.[13,14,40,43,44] Thus, increasing function and reducing or eliminating disability require careful vigilance for the presence or development of psychosocial factors. Because patients with chronic pain often lack adequate insight into their psychosocial situations, they will often underreport psychosocial issues. A careful evaluation

by a skilled psychologist and/or use of validated psychometric questionnaires will be more effective in determining the presence or absence of psychosocial comorbidities than a clinical interview.

Pursuit of disability is a common secondary gain issue. Disability determination should be carefully assessed by providers trained and skilled in functional evaluation. Disability should not be rewarded based on complaints of pain but based on objective physical impairments. A good example of this objective approach is the American Medical Association's *Guides to the Evaluation of Permanent Impairment*.[45]

Finally, it seems overly simplistic to assume that opioids will increase function through pain alleviation. Tolerance to the analgesic effect of opioids develops quickly in most individuals, diminishing safe therapeutic windows over time (well within the expected duration of chronic pain). Conversely, the presence of biopsychosocial comorbidities is common in the population with chronic pain, especially for people who are disabled. These comorbidities are risk factors for chemical coping (i.e., self-medicating psychosocial comorbidities), aberrant drug-taking behaviors, and substance use disorders. Oversimplification of pain by referring to it as a fifth vital sign, ignoring its behavioral aspects, and aggressively using opioids as a first-line treatment has greatly contributed to the current epidemic of prescription drug abuse and accidental lethal drug overdoses.[46]

## PHARMACOLOGICAL THERAPY

Currently, the pharmacological management of pain is mired in controversy. At the center of this controversy is the role of opioids in the treatment of pain. Frequently forgotten is the concept that the pharmacological treatment of pain should almost always start with nonopioid medications. The choice of drug should be dependent upon an understanding of the time course and pathophysiology of pain-producing processes.

### Nonopioid pharmaceuticals

For patients with acute musculoskeletal pain, the vast majority will improve significantly over the first month. If necessary, first-line pain medications should generally be a short course of an NSAID or a skeletal muscle relaxant (not including carisoprodol). Current best evidence indicates that these medications can provide measurable reductions in pain with an increase in function in the acute setting.[28,47] Special care must be taken when prescribing NSAIDs to patients with cardiovascular, gastrointestinal, and vasorenal risk factors. Unfortunately, opioids are all too frequently prescribed for acute musculoskeletal pain. A recent randomized controlled trial demonstrated that the addition of opioids to NSAIDs in patients with acute low back pain did not improve either pain or function at 1 week but was associated with increased side effects.[48]

For patients with chronic musculoskeletal pain, a multidisciplinary care plan is essential. Optimizing pain and function will require continued physical rehabilitation medicine and biopsychosocial treatments as discussed in previous sections. In the event that these therapies produce an inadequate response, it can be reasonable to consider chronic pharmacological therapy. As with the management of chronic musculoskeletal pain, treatment should almost always start with nonopioid medications. A recent randomized trial demonstrated a lack of efficacy for acetaminophen in both chronic spinal pain and pain related to osteoarthritis.[49] NSAIDs are the first-line drug of choice if medically appropriate.[28] Some guidelines have recommended opioids as a safer choice than NSAIDs for pain in people older than 75 years, given the gastrointestinal, renal, and cardiovascular risks associated with NSAIDs. However, there is a higher all-cause mortality among older people using opioids than among those using NSAIDs.[50] Recent data have also demonstrated that 200 mg/d of celecoxib was noninferior to ibuprofen or naproxen for cardiovascular outcomes. In addition, adverse gastrointestinal and renal events were lower in the celecoxib group.[51] Second-line drug therapy for chronic musculoskeletal pain includes duloxetine, tricyclic antidepressants, or occasionally tramadol.[28,47,52] Of note, tramadol is a weak opioid with abuse potential.

A unique class of patients includes those with neuropathic pain such as diabetic peripheral neuropathy, phantom limb pain, sciatica, spinal arachnoiditis, and postherpetic neuralgia. Among these patients, chronic treatment with NSAIDs is unlikely to produce significant pain reduction. First-line pharmacological treatments should focus on membrane-stabilizing medications such as gabapentin,[53] pregabalin,[54] tricyclic antidepressants,[55] duloxetine,[56] and topical local anesthetics.[57]

Considering a trial of opioids is a critical step in clinical decision making. This step should generally only be considered after multiple other therapies have failed and the patient is determined to have an appropriate risk profile using risk stratification techniques. Thus, given the significant risks associated with COT, this is an excellent time to consider referring the patient to a pain medicine specialist for a second opinion.

### The effectiveness of chronic opioid therapy

The US Congress proclaimed 2000 to 2010 to be the "decade of pain management," which helped increase public and medical awareness of pain management. Combined with a growing acceptance of opioid therapy among medical professionals in addition to a robust advertising campaign by opioid manufacturers, the last several decades have seen a surge in COT for the treatment of pain. Despite initial hopes, the efficacy of COT for the treatment of pain remains controversial. Several recent meta-analyses did not demonstrate a significant pain or functional change with COT.[8,58] Another meta-analysis of opioids for chronic low back pain observed a 50% dropout rate due to intolerable side effects or lack of effectiveness and concluded that pain relief from opioids was not consistently clinically meaningful at dose ranges from 40 to 240 morphine equivalents (MEQ) per day.[59] Unfortunately, very few clinical studies on opioids have evaluated time points after 12 weeks, making it incredibly difficulty to determine the long-term effectiveness. Given the complexities of pain

assessment, lack of evidence does not necessarily demonstrate lack of effect. However, it is difficult to rationalize the current national opioid prescribing patterns when the literature clearly illustrates the risk of COT while concurrently providing questionable evidence of benefit.

### The risks of chronic opioid therapy

Though studies of opioids may demonstrate short-term pain relief, there is no difference in function, sleep, or mood. In fact, the use of opioids has been associated with delayed recovery, increased disability, and lower function.[60,61] In a population study, only 16% showed an improvement in function when treated with opioids and the average opioid use increased quarterly, except among the few with functional improvement.[62] A Danish population survey discovered that people taking long-term opioids for chronic noncancer pain reported worse pain, lower quality of life, lower function, lower employment, and higher health care utilization compared with patients with chronic noncancer pain who did not use opioids.[63] Similar findings were observed in the United Kingdom.[64] These studies concluded that COT does not appear to meet the key outcome goal of functional improvement. It has been suggested that opioids worsen outcomes by promoting physical deactivation and apathetic mood.[65] In addition, opioid use may interfere with other treatments for chronic pain. For example, success rates for lumbar facet denervation for back pain were lower in patients receiving opioids.[66]

Older observational studies did not identify any impairment in driving related to opioids. However, a new population-based study demonstrated a dose-related risk of road trauma (i.e., motor vehicle accident) in drivers taking opioids chronically.[67]

Concurrent with the rise in opioid prescriptions, there was a staggering increase in opioid-related morbidity and mortality. The unfortunate utilization of opioids as a first step in the treatment of pain has both increased access to opioids and led to an increase in opioid addiction, abuse, overdoses, and drug-related deaths.[68,69] Unfortunately, accidental lethal drug overdoses from opioids continue to increase every year.[41,42] The rate of drug overdose deaths has risen from 12.3 per 100,000 in 2010 to 16.3 per 100,000 in 2015.[42] Tragically, physicians were the primary source of opioids leading to accidental lethal overdoses.[46,70] As expected, the total amount of diverted opioids is directly related to the total amount of prescribed opioids.[71] However, not all overdose victims are directly prescribed opioids. Many opioids reach their victims through diversion (transfer). Recent data estimate that 65.9% of nonmedical-use prescription pain relievers were obtained from friends and relatives.[72] Fortunately, opioid prescribing has been decreasing since 2011 but, unfortunately, deaths due to opioids continue to increase.[73] In 2010, oxycodone was the top drug involved in overdose deaths, but by 2014, it was ranked third behind heroin and cocaine.[74] Illegal drugs like heroin, cocaine, and illegally manufactured fentanyl are now responsible for more drug overdose deaths in the USA than prescription opioid medications.[74]

There is no universally accepted "safe" dose of opioids. In two studies, it was reported that risk of overdose death increases exponentially as the prescribed doses increase.[75,76] For example, an increase in MEQ from 20 mg/d to 50 mg/d (five 10-mg hydrocodone tablets per day) doubles the risk of an opioid overdose, and an increase to 90 mg MEQ per day increases the risk of an overdose by nine times.[77] In addition, the risk of overdose death increases with the addition of a long-acting opioid.[78] Mixing opioids with other central nervous system depressants, such as carisoprodol and especially benzodiazepines or alcohol, synergistically increases the risk of accidental lethal overdoses.[41,42,77,79] Additionally, prescribers should be aware that the availability of opioids in a household poses a danger of diversion and accidental overdose to family members, especially children and adolescents.

Sadly, 91% of patients who survive an opioid overdose are represcribed opioids and 17% of overdoses are not the victim's first overdose.[80] An overdose is a clear indication that opioids should be discontinued, not restarted. These facts suggest a lack of appropriate risk assessment prior to starting opioids and inadequate monitoring of COT. Along with monitoring the long-term physiologic consequences of COT, the standard of care for physicians who prescribe COT is to employ appropriate risk assessment tools and closely monitor patients for misuse, abuse, and diversion.[3] This topic is discussed in more detail later in this article.

### 2016 Centers for Disease Control and Prevention guidelines

Given the well-documented risks associated with COT and the opioid overdose epidemic, in 2016 the Centers for Disease Control and Prevention (CDC) issued guidelines for primary care providers when prescribing opioids for the treatment of chronic pain.[79] This guideline was written to specifically exclude the role of opioids in active cancer care and palliative settings. The fundamental tenet of this document is that comprehensive pain management should take a multimodal and multidisciplinary approach. Rehabilitation treatments, psychological assessment and treatment, nonopioid pharmaceuticals, and interventional procedures should all be considered prior to initiating COT. In addition, risk stratification and continued monitoring are absolutely essential if COT is utilized. All physicians who prescribe opioids should be well versed in the 2016 CDC guidelines.

### Side effects and complications of COT

Opioids can produce a wide array of side effects following both acute and chronic usage. This is evidenced by the fact that opioid therapy trials have a dropout rate between 20% and 50% due to intolerable side effects or lack of efficacy.[65] In addition to the previously known risks of COT (tolerance, addiction, cognitive impairment, and constipation), recent literature has identified other potential complications of COT, including opioid-induced endocrinopathies, opioid-induced hyperalgesia, depression, and death from central sleep apnea.

### Opioid-induced endocrinopathies

COT produces a dose-dependent central hypogonadism state in both men and women. The hypogonadism mechanism appears to be direct inhibition of gonadotropin-releasing hormone release. For women, COT can result in 48% to 57% reductions in estradiol and dehydroepiandrosterone sulfate.[81] Similarly, men experience significant reductions in testosterone production with COT. Decreased serum testosterone levels and COT are associated with osteoporosis and osteoporotic fractures. More specifically, 50 MEQ morphine per day (the equivalent of 5 Norco 10 mg per day) was associated with a twofold increase in osteoporosis-related fracture risk and a 10% increased annual risk of fracture in the elderly.[28,82] Low serum testosterone levels are also associated with depression, anxiety, and lower quality of life.[83]

Symptoms suggestive of hypogonadism include loss of libido, impotence, infertility, depression, anxiety, loss of muscle mass and strength, loss of gender role, fatigue, amenorrhea, irregular menses, possibly galactorrhea, osteoporosis, osteoporosis-related fractures, and lower pain threshold. Unfortunately, these symptoms are common in patients with chronic pain, even without abnormal sex hormone levels. Therefore, individuals using COT should be assessed for gonadal function, and all at-risk individuals should have bone mineral density measurements. Because endocrine supplementation is complex, referral to an endocrinologist may be prudent.

### Opioid-induced hyperalgesia

Opioids are powerful analgesic agents in the short term. Opioids attenuate the nociceptive experience by interacting with both central and peripheral mu (opioid) receptors. Unfortunately, persistent nociceptive experiences are associated with DNA activation of previously inactive genomes, resulting in protein synthesis and expression of numerous previously unavailable receptor complexes, thus allowing maladaptive intercellular communications. As a result, multiple receptor interactions are involved in the production and communication of chronic nociceptive pain perception. Therefore, pharmaceutical manipulation of opioid receptors may not be the best route to produce analgesia in a chronic pain state.

In the last several years, laboratory and clinical research has provided compelling evidence that opioid exposure can create an abnormally low pain threshold (sensitivity). There is new evidence suggesting that hyperalgesia and allodynia may occur while on uninterrupted opioid therapy. Clinically, opioid-induced hyperalgesia is similar to the development of opioid tolerance (i.e., the need for a dose increase for the same analgesic benefit). Clinical indicators suggesting opioid-induced hyperalgesia include chronic requirement for high-dose opioids, poor function and quality of life despite reasonable doses of opioids, expansion of pain to previously nonpainful sites, and escalation of pain complaints in parallel to opioid dose increases.

Hyperalgesia can develop rapidly. It has been observed within 1 week or even after a single exposure to opioids in laboratory animal models. Therefore, patients prescribed COT would benefit from a referral to comprehensive pain management specialists for evaluation and consideration of other modalities of care. Perhaps the best option is to reserve COT for well-selected individuals who have been compliant with multimodal therapies and quality multidisciplinary functional restoration attempts but failed to make adequate progress.[84–86]

### Opioid-induced central sleep apnea

Opioid-induced respiratory depression tends to be a short-lived phenomenon. It generally occurs only in the opioid-naïve patient. Recent data suggest that COT increases the risk for central sleep apnea and may aggravate obstructive sleep apnea.[87] Chronic benzodiazepine use also increases central sleep apnea risk. This risk is potentiated when opioids and benzodiazepines are combined. Tolerance to central sleep apnea or obstructive sleep apnea does not occur. Opioid-induced central sleep apnea is a potential cause of unexplained accidental deaths among patients treated with COT and/or benzodiazepines. Thus, significant risks exist with COT, particularly in patients with sleep apnea who take benzodiazepines. Coadministration of opioids with other central nervous system sedatives, especially benzodiazepines, should be avoided.[41,42,88]

### Opioid-induced mood disorders

Opioid use has been found to cause depression, and recent studies have demonstrated that new-onset depression is directly related to both dose and duration of exposure.[89,90] In addition, depression can be triggered by a rapid escalation in opioid dose.[91] Therefore, both pain and opioid analgesic use must be considered as potential sources of depressed mood. The patient's depression may not respond to therapy until his or her opioids are discontinued.

### Opioid misuse and abuse

The incidence of aberrant drug-taking behavior in the chronic pain population is very difficult to determine. This stems in part from a reluctance of those misusing or abusing opioids to readily admit it to their physician. A proxy measurement for misuse and abuse is the frequency of urine drug tests (UDTs) that are inconsistent with the specific pain prescription for the patient. The incidence of aberrant UDTs is surprisingly high with a range of 9% to 47%, with most studies reporting near 30%.[92] Aberrant UDTs may represent many problematic behaviors, including addiction and chemical coping. Clearly, it is a good standard of care to screen for risk factors predictive of aberrant drug-taking behavior prior to initiating COT. Aberrant drug-taking behavior is a patient and public safety concern requiring corrective action. Therefore, UDT is the standard of care when treatment involves COT.[3]

Risk factors associated with aberrant drug use have been identified by numerous studies and include the following[92]: personal or family history of alcoholism or substance abuse

(past or present), nicotine dependency, age less than 45 years old, depression, anxiety, impulse control problems (attention deficit disorder, bipolar, obsessive-compulsive disorder, schizophrenia, personality disorders), hypervigilance states (posttraumatic stress disorder, preadolescent sexual abuse, history of or ongoing abuse), somatoform disorder, organic mental syndrome, pain after accidents (secondary gain issues), and pain involving more than three regions of the body.

### Screening metrics

Screening metrics are available for stratifying COT risk factors. The Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain (SOAPP) and revised SOAPP (SOAPP-R) are the most widely accepted tools for opioid risk assessment. The CAGE questionnaire and other screening tools can assess problematic alcohol use. The Texas Pain Society recommends the SOAPP-R, because the current evidence demonstrates that the SOAPP-R is superior in identifying those at high risk.[92]

Therefore, the presence of unstable biopsychosocial factors and/or history of substance abuse are relative contraindications for the use of COT. Unfortunately, patients with unstable biopsychosocial factors are those most likely to be prescribed COT.[93,94]

### Prescription monitoring programs

Prescription monitoring programs have the ability to provide quasi-real-time dispensing data about a patient's use of controlled substances. Once the database became available to clinicians online, it became a powerful tool to identify aberrant drug-taking behavior or the presence of dangerous drug combinations (i.e., cocktails). In addition, prescription monitoring programs are a powerful tool to help physicians identify patients who may be doctor shopping and or diverting opioids (transferring them to others).

### Pharmacological conclusions

In conclusion, the appropriate utilization of pharmacological therapies for the treatment of pain requires an understanding of both the nature of the pain and the type of person experiencing the pain. First-line drugs for the treatment of pain should almost always be nonopioids. Opioids can be used in a limited fashion for serious acute injuries but should be discontinued as soon as possible (the CDC recommends 3 to 7 days). COT may be a friend to some, but is a foe to many. Only an unknown fraction of patients with chronic pain will benefit from COT. The majority will experience more risk and harm than benefit. COT appears to delay recovery and promote declining function for many. Only well-selected patients appear to benefit from COT. Careless (i.e., below the standard of care) opioid prescribing results in many unintended consequences for patients and society. Ignoring the biopsychosocial aspects of pain ultimately comes at the patient's peril. Pain is never listed as a cause of death, but accidental/unintentional opioid overdoses (prescription and illicit) are listed as a cause of death at alarming and ever-increasing rates.

## INTERVENTIONAL TREATMENTS

In the last 25 years, there has been a tremendous increase in procedures for the treatment of pain. The ideal time to perform a pain procedure is generally following a good faith trial of conservative management. One of the advantages of interventional procedures is that they may prevent some of the risks and side effects associated with pharmacotherapy options, particularly opioids. Unfortunately, following the initiation of opioids, procedural interventions can be less effective.

Due to a surge in clinical research, numerous randomized controlled trials have demonstrated the efficacy of many pain procedures. There is good to excellent evidence to support the following procedures: medial branch denervation for the treatment of zygapophyseal (facet) pain,[95] genicular nerve denervation for the treatment of knee pain,[96] epidural steroid injections for the treatment of acute radicular pain,[97] chemodenervation with botulinum toxin for the treatment of headaches,[98] vertebral augmentation for the treatment of painful acute vertebral compression fractures,[99] and spinal cord stimulation or intrathecal drug delivery devices for the treatment of persistent back and leg pain.[100,101]

## CONCLUSION

In conclusion, the treatment of chronic pain is important, but it is also extremely important to deliver safe and effective treatments using evidence-based treatments as first-line strategies. Fortunately, there are evidence-based treatments for chronic pain that are conservative therapies: exercise and cognitive-behavioral therapy. Unrecognized and unstable biopsychosocial comorbidities are common in the population with chronic pain, particularly in the poorly functioning population with chronic pain. Unstable biopsychosocial comorbidities are barriers to recovery and risk factors for aberrant drug-taking behaviors. The best treatment strategies for chronic pain involve an interdisciplinary/multidisciplinary approach.


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