Module 7 Assessing and Treating Persistent Nonmalignant Pain: An Overview

Original Release date: September, 2007 Updated: February, 2010 Expiration Date: March, 2012

Unrelieved chronic or persistent pain is a significant public health problem in the U.S., with prevalence estimates ranging from 15% to 30%.[1] A World Health Organization (WHO) survey of primary care patients found 21.5% suffered severe pain for most of a 6-month period during the previous year.[2] Persistent pain significantly impacts quality-of-life and is often accompanied by anxiety, depression and sleep disorders, all of which complicate management.

Educational Objectives

- Utilize a basic approach to the evaluation and assessment of the patient with persistent nonmalignant pain.
- Apply the basic nonpharmacological and pharmacological approaches to the management of persistent pain.

The American Medical Association designates this education activity for a maximum of 1 AMA PRA Category 1 Credit™. Physician should only claim credit commensurate with the extent of their participation in the activity.

This continuing medical education program is intended for primary care physicians and those physicians who care for patients experiencing pain.

Financial Support
This CME module is supported through an unrestricted educational grant from Purdue Pharma L.P. and produced in accordance with the AMA Standards for Industry-Supported Multimedia Continuing Medical Education and Other Communications.

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Pain is one of the most common reasons for patients to seek medical attention and one of the most prevalent medical complaints in the US.[1-3] According to the 2006 National Center for Health Statistics Report, one in 10 Americans overall and three in five of those 65 years or older said that they experienced pain that lasted a year or more.[2] More than one-quarter of adults said they had experienced low back pain, and 15% of adults experienced migraine or severe headache in the past three months. Between the periods 1988-94 and 1999-2002, the percentage of adults who took a narcotic drug to alleviate pain in the past month rose from 3.2 percent to 4.2 percent.

For the the millions of Americans who experience persistent pain, the impact on function and quality of life can be profound.[2-4] Pain is associated with high utilization of health care[4] and the societal costs related to treatment are compounded by the loss in productivity associated with persistent pain. Lost productive time from common pain conditions among workers costs an estimated $61.2 billion per year and most of this is related to reduced performance while at work.[5] The total annual cost of poorly controlled persistent pain most likely exceeds $100 billion.

Physicians and other clinicians need current, state-of-the-art education to assist them in developing the necessary skills to evaluate and manage patients with persistent pain. This CME program reviews assessment and management of persistent pain syndromes that are frequently seen in primary care.

1. Watkins EA, Wollan PC, Melton LJ 3rd, Yawn BP. A population in pain: report from the Olmsted County health study. *Pain Med.* 2008;9(2):166-74.

2. http://www.cdc.gov/nchs/hus.htm

3. Blay SL, Andreoli SB, Gastal FL. Chronic painful physical conditions, disturbed sleep and psychiatric morbidity: results from an elderly survey. *Ann Clin Psychiatry.* 2007 Jul-Sep;19(3):169-74.

4. Von Korff M, Lin EH, Fenton JJ, Saunders K. Frequency and priority of pain patients' health care use. *Clin J Pain.* 2007 Jun;23(5):400-8.

5. Stewart, WF, Ricci, JA, Chee, E, Morganstein D, & Lipton R. (2003). Lost productive time and cost due to common pain conditions in the US workforce. *JAMA.* 2003; 290(18);2443-2454.

Introduction

The term persistent, or chronic, pain conventionally refers to pain that is not associated with cancer or some other serious medical illness and has continued for more than 3 to 6 months. An alternative definition indicates that chronic pain is any pain that persists for at least one month beyond the usual course of an acute illness or typical healing time following injury, pain associated with a persistent pathologic process; or pain recurring at frequent intervals for a period of months or years.[1,2]

Persistent pain often is associated with physical and psychosocial functional impairments, a complex relationship with underlying disease and varied comorbidities. Some patients develop a high level of disability, and treatment must focus as much on functional restoration as comfort. The complexity of the pain-disability nexus justified the development of a multidisciplinary approach, which applies a multimodality therapeutic strategy that may include a range of interventions, including drug therapy, cognitive and behavioral therapy, physical rehabilitation, and sometimes, more invasive modalities such as injections. Management goals include restoration and/or improvement of function, mood and sleep patterns, and a realistic reduction in pain severity.

Physiology of Persistent Nonmalignant Pain

Persistent nonmalignant pain is often multifactorial in origin. Numerous pathophysiologic processes subsumed by clinical labels— "nociceptive" and "neuropathic" and may be involved, and co-existing psychological process may act to influence pain severity and modulate its impact on multiple domains of function and quality of life.

Pain may or may not be out of proportion to overt evidence of tissue injury. In some cases, the clinical findings support the conclusion that the pain is related to the disordered physiological processes involved in neuropathic pain, in which dysfunction in the peripheral or central nervous systems, or both, sustain the pain even in the absence of ongoing injury. In other cases, there is positive evidence that psychological processes, sometimes meeting the criteria for specific psychiatric disorders, are the primary drivers of sustained pain. Finally, there may be no adequate explanation for the pain, in which case it is best to label it "idiopathic" and intend to continue the evaluation over time.

The distinction between nociceptive and neuropathic pain represents a clinical inference about the pathophysiology that is likely to be sustaining the pain. Nociceptive pain implies that there is some ongoing source of tissue injury, either somatic or visceral, that continues to activate intact neural structures and cause pain.[3] Although ongoing tissue injury undoubtedly leads to profound neuroanatomic, neurochemical and neurophysiological changes, the inference clinically is that the persistent afferent input originating from a specific peripheral source is the primary cause of the pain. One important implication of this inference is apparent: If treatment can be directed to the source, and attenuate the nociceptive input that it produces, pain will improve.

In contrast to nociceptive pain, neuropathic pain now is best understood from a paradigm of neuronal plasticity. Precipitated by peripheral trauma or other factors, changes occur within the dorsal horn of the spinal column, sensory thalamus and cerebral cortex, which persist beyond the resolution of the trauma. Persistent pain perception is associated with both genotypic (*e.g.*, up-regulation of genes for sensory neuron-specific channels) and phenotypic changes that occur at all levels of pain signal processing from primary afferents to the cerebral cortex.[4] Because of the wide variety of neurotransmitters (*e.g.*, substance P, serotonin, prostaglandins, bradykinin, leukotrienes, histamine, norepinephrine) and receptors (*e.g.*, opioid, serotonin, acetylcholine, dopamine, norepinephrine) involved in pain pathways, many potential targets for drug therapy exist.

Evaluation & Assessment of the Patient with Persistent Pain

Pain experts now strongly endorse a key concept: When pain becomes persistent, it is best conceptualized as an illness in its own right. Although it is true that some patients with persistent pain have identifiable diseases or activities that generate pain, much as acute pain is associated with specific causes, the lived reality of pain every day exacts such a profound toll on most individuals that it is better to approach the clinical problem from an "illness" perspective. "Pain as illness" implies that the clinicians must supplement an assessment of the underlying cause with an assessment of the broader impact of the pain itself on all functional domains—physical, psychological, social and others.

Persistent nonmalignant pain also must be conceptualized as a broad clinical group of syndromes and disorders, idenfication of which through a detailed assessment may lead to options for specific therapies, as well as a broader symptomatic approach (see module 1).

Several considerations should guide the assessment of patients reporting persistent pain.[5-7] Characterization of the pain and its cause—when possible—should be a routine part of any patient assessment and is essential in guiding management strategies. The ways in which pain affects physical function, psychosocial function, and other aspects of quality-of-life should be considered a routine part of the comprehensive pain assessment.

Pain History and Physical Examination

A thorough pain history includes obtaining information about thecharacteristics of the pain. This process is sometimes facilitated by reference to the nmenonic "PQRST:"

PQRST

P – what **provokes** (makes it worse) and what **palliates** (makes it better) the pain?

Q – what **quality** is the pain (*e.g.*, aching, stabbing, burning)?

R – what **region** is affected (specifically: the primary location, the pattern of radation, and whether the pain is deep or superficial)?

S – what **severity** is the pain (typically 2 questions: How severe has the pain been on average during the past week? How severe has the pain been at its worse during the past week?)?

T – what are the **temporal** characteristics (specifically: onset [acute or insidious], duration, course [getting better, stable or getting worse], and daily fluctuation)?

The pain history should focus on the relationship between the pain and the medical conditions known to the pain. The patient may be the expert, helping the physician understand whether the pain may be explained by an understanding of the current status of another illness, such as cancer or rheumatoid arthritis.

The history also should evaluate the impact of the pain on all the relevant domains of the patient's quality-of-life. This may start with a general question: How has the pain affected your function and quality of life? Specific questioning follows about the extent to which the pain impairs physical function. This may include reference to activities of daily living and exercise, and also questions about related symptoms, such as insomnia, fatigue, mental acuity, and others. Because sleep disturbance is a frequent complicating factor in persistent pain, it is particularly important to inquire about the patient's sleep patterns. Patients with pain, particularly if it is persistent, often experience less deep sleep, more arousals with waking, and overall, less efficient sleep; it is estimated that over half of persistent pain sufferers have trouble falling and staying asleep.

Questions about psychological and psychosocial functioning should focus on mood (particularly depressed mood and the ability to experience joy, and anxious mood), coping, impact of pain on the marriage or intimacy, and impact of the pain on the ability to socialize.[8,9] Because the incidence of depression in patients with persistent pain may exceed 80%,[6,7] the initial evaluation should include assessment for depression or other psychological comorbidities. One of the objectives of the pain assessment is to determine whether an associated mood disorder is severe and persistent enough to reach a threshold for a diagnosis with clear treatment implication, such as major depression, generalized anxiety or panic disorder. If this is the case, and a psychiatric comorbidity is suspected or diagnosed, appropriate referral to a mental health professional should be considered.

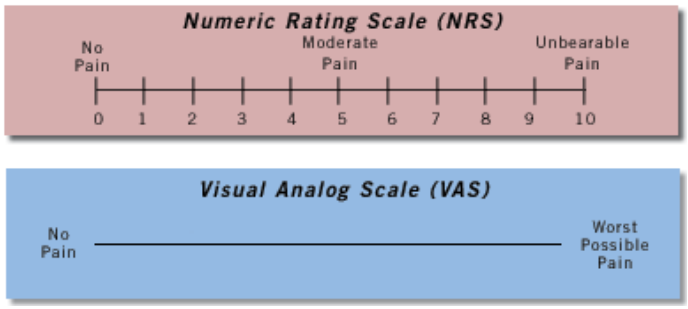
In asking about the impact of the pain on physical and psychosocial functioning, it is essential to query the effect on so-called role functioning: Has the patient been working or is the patient receiving disability payments? Has functioning in the family been compromised? What about the role as patient; has this become a full-time job?

The health history also should include a complete medication history, including all current and previously used prescription and OTC analgesic medications (noting their effectiveness and adverse effects), as well as any alternative or complementary therapies. A drug use history is essential and should specifically query the present and past use of analgesic drugs, alcohol, and illicit drugs. In addition, the medical history should especially focus on any influential comorbid diseases and aspects of physical function that may cause or exacerbate persistent or acute pain.

In the course of the initial pain evaluation, physicians and other clinicians should demonstrate their acceptance of the patients' self-report of pain and their willingness to investigate its cause. Although physicians know that malingering and factitious disorders exist, they are rare in relation to the enormous problem of persistent pain that is truly experienced (whether or not there is sufficient evidence of bodily dysfunction to diagnose it in biomedical terms). The appropriate stance, therefore, is to simply believe that the patient is truly experiencing the symptoms reported, recognizing that this does not preclude an understanding of the experience as driven, in part or mostly, by psychological factors and also recognizing that believing the patient dose not imply the need for any type of specific therapy. Therapeutic decision making, although grounded in the patient's history, represents the outcome of an evaluation of a broader set of data.

As part of the comprehensive evaluation, careful examination of the site of reported pain, including palpation for trigger and tender points, swelling and inflammation, and range of motion testing should be conducted. The neurological examination should include assessment for signs of sensory, motor and autonomic dysfunction that may suggest neuropathic pain.

Obtaining and reviewing the patient's past medical records is part of a good evaluation. This is particularly important if there are uncertain diagnostic features to the pain or its impact, or if the plan of care may include treatment with a controlled prescription drug. The history, including past records, may highlight the need for specialized services—such as substance abuse treatment—which should lead to a referral when feasible.



Tools for Assessing Persistent Pain

Pain measurement is an important part of the more comprehensive pain assessment and can be accomplished in many ways. The selection of a tool should be based on the care setting, patient characteristics (*e.g.*, age, cognitive ability, functional status), and other relevant considerations. Unidimensional pain scales such as the Verbal Rating Scale, the Numeric Rating Scale, and the Visual Analog Scale are useful in assessing pain intensity, are easy to administer, and are sensitive to treatment effects.10-12 For multidimensional assessment, the Brief Pain Inventory (BPI) is commonly used in persistent pain conditions; the BPI is easily administered and provides information on pain history, intensity, location, quality, and functional status.[13]

Evaluating function is critical in patients with persistent pain, as improved function is one of the principal goals of therapy. The functional assessment may include biomedical factors, such as joint range of motion, posture, gait, or balance; simple functional elements, such as activities of daily living (ADLs such as bathing, dressing, using the toilet, continence and eating); more advanced ADLs (known as instrumental ADLs, such as shopping or cleaning); or yet more complex types of functioning, including work, avocations, and social interactions. While most functional assessment tools require special training to administer and are not commonly used in the primary care setting, clinicians should be aware of their use. The BPI provides some information on the impact of pain on function; it does not specifically measure performance status or ADLs. Other tools, such as the Functional Reach Test[14] and the Katz Activities of Daily Living[15] have been developed for this purpose.

Given the importance of mood, coping, pain beliefs, feelings of helplessness and catastrophization, social support, family relationships, work history, and other factors, measurement of some of these elements may be valuable using multidimensional tools. There are numerous multidimensional scales, each measuring different aspects of pain-related disability, specific functional concerns, or health-related quality of life. For example, the Multidimensional Pain Inventory examines the patient's perceptions, emotions and behaviors (including coping strategies) associated with pain,[16] and the Treatment Outcomes of Pain Survey (TOPS) is a pain-enhanced version of the gold standard health-related quality of life (HRQoL) instrument known as the Medical Outcomes Study Short Form 36 (MOS SF-36 or SF-36).[17] At the present time, these scales generally are used in research.

Management of Persistent Nonmalignant Pain

Although the label "persistent nonmalignant pain" often is taken to imply that the patient has no potentially reversible biomedical pathology, it is best to make judgment an explicit part of the evaluation. The comprehensive assessment of the patient, including the history, physical examination, and review of records, should lead to a diagnostic formulation, which in turn is the basis for the initial plan of care. The diagnostic formulation may include the following:

1. clinical hypotheses about the etiology (the biomedical causes), the pathophysiology (inferences about the sustaining mechanisms, *e.g.*, nociceptive, neuropathic, psychogenic or some mix), and the appropriate syndromic label;
2. understanding about the broader nature and impact of the pain, such as the extent to which the pain is associated with particular problems such as depressed mood or catastrophization, or with the inability to function in particular contexts, or with a more global disability; and
3. relevant concurrent symptoms, such as insomnia, or physical or psychiatric comorbidities.

The plan of care should begin with a determination of the need for more data to confirm or clarify elements of the diagnostic formulation. It may not be possible to develop an adequate treatment approach until tests are done or records are obtained.

The plan of care also begins with consideration of primary disease-modifying therapy. If the etiology of the pain is determined and a treatment is available, appears acceptable from the perspective of risk and benefit, and is consistent with the goals of care, then it should be strongly considered as part of the pain-related therapeutic strategy.

From the start, the plan of care also should consider treatments for relevant comorbidities. Great progress can be made in the care of the disabled persistent pain patient by meaningfully addressing such problems as a comorbid sleep disorder or major depression.

At the same time that these elements of the plan of care are pursued, patients with persistent pain should be offered the first steps in a therapeutic approach intended to enhance comfort and function. Patients who are involved in their pain management plan and who understand and accept responsibility for their health typically have the best response to medical interventions. There are many potential therapeutic strategies (see Table) that may be developed into a multimodality approach guided by appropriate and realistic goals for the patient. These goals typically include: reducing the pain severity while improving and/or restoring function and mood. Additional treatment goals may include: (1) reducing misuse or overuse of medication; (2) returning to productive activity at home, socially, and/or at work; (3) increasing the patient's ability to self-manage pain and related problems; (4) reducing or eliminating the use of ongoing healthcare services for the primary pain complaint; and (5) minimizing treatment cost without sacrificing quality of care. In many cases, improved physical and psychosocial functioning may be the most important goal for monitoring treatment success.[18,19]

Table: Categories of Pain Treatments

Drug	Comment
Pharmacologic	Nonopioid drugs Opioid drugs Adjuvant analgesics
Rehabilitative	Physical and occupational therapy Modalities (heat, cold, ultrasound, electrical stimulation)
Psychological	Cognitive-behavioral therapy Specific treatments (e.g., biofeedback) Other types of psychotherapy
Complementary and Alternative	Acupuncture, massage, chiropractic, nutraceuticals / botanicals, energy therapies, non-Western systems (traditional Chinese medicine)
Interventional	Injection therapy (*e.g.,* spinal injections, other needle-based therapies, trigger point or joint injections) Neural blockade (*e.g.*, stellate ganglion block, regional anesthesia techniques) Implant therapies (*e.g.*, spinal cord stimulator, peripheral nerve stimulation, neuraxial analgesia via pump)
Surgical	Neurectomy, nerve decompression, cordotomy

The multimodal approach to persistent pain management includes the use of numerous therapeutic modalities. Psycho-educational strategies, cognitive-behavioral therapies, and rehabilitation approaches should be considered in all cases, along with appropriate pharmacologic therapy, selected complementary and alternative therapies, and occasionally, interventions such as injections. An individualized treatment plan should be developed for each patient.

Tools to Address Psychosocial Considerations

- West Haven-Yale Multidimesional Pain Inventory
- Survey of Pain Attitudes (SOPA)
- Barriers Questionaire
- Pain Stages of Change Questionaire (PSOCQ)

Patient and Caregiver Education

An important component of setting realistic pain-relief goals is patient education. All educational activities should be sensitive to culture, ethnicity, and the values and beliefs of individual patients and their families. Patient education includes discussion of the goals of therapy and provides information about pain and its assessment and methods for pain relief. Patient education should also address patient fears, barriers to pain management, and any misconceptions the patient may have about the cause or treatment of their pain.

Patients and/or caregivers might be educated about the use of a pain diary to record pain intensity, associated activities that may exacerbate their pain, medication use and response to treatment; information from the diary may help guide management strategies.

Online Patient Education Resources

JAMA Patient Pages
- Pain Management
- Headaches
- Osteoarthritis of the Knee
- Coping with Back Pain

Medem
- Arthritis and Exercise (NIH)
- Chronic Pain: When Surgery is Not the Answer (American Association of Neurological Surgeons)

Organizations for Patients
- American Council for Headache Education
- American Chronic Pain Association
- American Pain Foundation
- Arthritis Foundation
  - Understanding Your Pain
  - Taking Control of Arthritis Pain
- Harvard Health
  - Pain and Depression

Cognitive-Behavioral Therapy

In the treatment of persistent pain, cognitive-behavioral therapy (CBT) can be broadly defined as interventions that change behavior, thoughts or feelings to help patients experience less distress and enjoy more satisfying and productive daily lives.[20] Through CBT, patients learn to identify—and change—dysfunctional beliefs and attitudes that adversely affect their ability to cope with pain. Motivating the patient to increase their activity, reduce their social isolation, interact with others, and engage in pleasurable activities are important components.

Persistent pain sufferers may demonstrate negative thoughts, which can be related to the emotional difficulty of living with pain. Common patterns include overgeneralization, catastrophizing, all-or-none-thinking, jumping to conclusions, selective attention, and negative predictions. In the treatment of persistent pain, one of the most established interventions is cognitive-behavioral therapy (CBT).[18-22] Three goals of BT-CBT for pain management are to: (1) help patients understand that their thoughts and behaviors can affect the pain experience, emphasizing the role they can play in controlling their own pain; (2) train patients in effective coping skills; and (3) apply and maintain their learned coping skills. The specific strategies may include education; training in cognitive therapies such as biofeedback, relaxation and imagery; and specific behavioral treatments such as graduated exercise, pacing and time management and sleep hygiene training. The table, Common Components of Behavioral and Cognitive-Behavioral Treatment of Persistent Pain provides more details. Through CBT, patients learn to identify—and change—dysfunctional beliefs and attitudes that adversely affect their ability to cope with pain. Motivating the patient to reduce their social isolation, interact with others, and engage in pleasurable activities is another important component.

Common Components of Behavioral and Cognitive-Behavioral Treatment of Persistent Pain

- Promotion of a self-management perspective
- Relaxation skills training
- Cognitive therapy; also known as cognitive restructuring or self-statement analysis
- Behavioral activation and management, including goal-setting and pacing strategies
- Problem-solving skills training
- Other interventions to change perception or emotional response to pain, such as guided imagery, desensitization, hypnosis, or attention control exercises
- Communication skills training or family interventions
- Habit reversal
- Maintenance and relapse prevention

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CBT may be conducted in individual therapy or in small group sessions of 4 to 8 patients. Both approaches have been effective in clinical trials.[18] CBT is not suitable for patients with substantial cognitive impairment, and healthcare professionals need to have specialized training in CBT to use it effectively.

Behavioral Therapies

There are a variety of specific behavioral therapies that may be used independently or incorporated into a CBT strategy for chronic pain. They include biofeedback, relaxation training and hypnotherapy.

Biofeedback

In biofeedback, the patient is trained to change specific physical parameters to reduce undesirable symptoms. Biofeedback is a noninvasive form of treatment, requiring little effort; however, it does require a trained professional to control monitoring equipment. Sensors or electrodes attached to the patient's body provide 'feedback' measuring skin temperature, muscle tension, and/or brainwave function. With this information, patients learn to make subtle changes, and with practice, new responses and behaviors can help to bring relief and improvement.

Relaxation and Imagery Training

Expert review of relaxation techniques concluded that pain reduction occurs through a decrease in oxygen consumption, a lowering of blood pressure, respiratory rate, and heart rate, an increase in EEG slow brain waves, and possibly reduced awareness of pain.

There are numerous techniques to achieve relaxation. Some may be utilized by nonspecialists. Some of the common types follow:

1. Breathing patterns that potentiate relaxation.
   - Patient may be instructed to take slow, deep breaths with exhalation lasting longer than inhalation
   - Technique is practiced for 5 to 10 minutes/day

2. Progressive muscle relaxation
   - The patient is instructed to tense and then relax muscles in one region of the body.
   - Patient learns to recognize undesirable tension in the body and relax it.

3. Guided imagery
   - The patient is directed to recall or create a pleasant and relaxing image
   - Patient focuses attention on the sensory details of image (*e.g.*, sensations of light, color, sound, texture)
   - Technique intended to provoke a quick relaxation response and a brief respite from a stressful situation
   - May be used with deep breathing exercises and progressive muscle relaxation.

Hypnotherapy

A more complex technique than relaxation therapies, hypnosis requires specialized training for both the practitioner and patient. Hypnosis assists patients in obtaining deeper levels of relaxation, which often leads to more peaceful sleep, increased energy, and diminished pain. Research has not yet been able to delineate the mechanism underlying hypnosis' effect, but it appears to be more effective than placebo.[23] Analgesia produced through hypnosis requires the patient's full cooperation, and some patients are more susceptible to hypnosis than others.

Physical Rehabilitation and Exercise

Physical rehabilitation is a particularly common treatment for pain and is often instituted as one component of a multidisciplinary strategy in many persistent pain syndromes. Graded exercise programs seek to reverse or prevent deconditioning that may preclude function, contribute to fatigue, or predispose to new musculoskeletal sources of pain.

Many patients with persistent pain may restrict their physical activity in the belief that activity exacerbates their pain, or that they are in imminent danger of harming themselves if pain is provoked by activity. This belief system, which is summarized as "hurt equals harm" can undermine efforts to improve functioning. Once serious underlying physical pathology has been excluded, patients should be educated that "hurt does not equal harm;" in fact, when physical deconditioning is reversed with gentle and appropriate exercise, pain levels may decrease. Moderate levels of physical activity should be maintained—even if the pain persists—and the program should include exercises that improve flexibility, strength, and endurance.

Coupling certain CBT strategies designed to enhance communication, control, problem-solving and coping with advice to exercise can have a clinically significant impact on reducing pain and improving functional status.[19,20] Physical therapists may set functional goals for the patient, such as being able to walk a certain distance or duration, carry a certain amount of weight, or perform essential job tasks. Because engagement in a moderate exercise program should be life-long, programs should take into account patient preferences, which will promote compliance. Finally, when prescribing exercise, it is important to review the patient's medications for agents that may increase the risk of falls (*e.g.*, psychotropic agents, diuretics, antihypertensives).

Cutaneous Stimulation

So-called modalities (heat, cold, ultrasound, electrical stimulation and massage) often are listed among the rehabilitative strategies used in the treatment of chronic pain. Patients with regional pain, particularly musculoskeletal pain, may find superficial heat or cold (*e.g.*, hot-water baths, ice packs, vapocoolant sprays) brings some relief; hot or cold treatments should not be applied to areas with diminished sensation or in patients who are unable to communicate. Some data suggest that massage therapy can be an effective component of a pain management plan (specifically for relief of persistent low back pain or to reduce the incidence of persistent tension headaches). Therapeutic massage is thought to transiently alter physiological responses and induce relaxation.

Transcutaneous Electrical Nerve Stimulation (TENS)

Some patients report analgesic effects when treated with transcutaneous electrical nerve stimulation (TENS). This neurostimulatory approach uses low electrical current applied to the skin. Although the evidence continues to be relatively weak[24] there is extensive experience suggesting that TENS can reduce pain in selected patients.

Complementary and Alternative Medicine

A large proportion of patients with persistent pain make use of one or more complementary and alternative medicine (CAM) approaches, often while concurrently pursuing allopathic therapies. As defined by the National Institute of Health's National Center for Complementary and Alternative Medicine (NCCAM), CAM therapies are a group of diverse medical and health care systems, practices and products that are not presently considered to be part of "conventional medicine," and while some scientific evidence exists regarding CAM therapies, most are associated with questions about efficacy that are yet to be answered through well-designed scientific studies.

Nonetheless, some therapies that are labeled CAM are considered "mainstream" by pain specialists. Because many patients are using these therapies, it is important to inquire about all interventions patients have employed, and to encourage patients who embrace these therapies to integrate CAM into broader management strategies most likely to provide relief without doing harm.

Manipulative Methods

These methods are based on manipulation and/or movement of one or more parts of the body, and include chiropractic spinal manipulation. Chiropractic therapy focuses on the relationship between bodily structure and function, and how that relationship affects the preservation and restoration of health. There have been many randomized controlled clinical trials (RCTs) studying the effectiveness of spinal manipulation in the relief of spinal pain, the majority of which have looked at acute low back pain. Most of the studies investigating the effectiveness of manipulation on chronic low back pain have reported short-term positive results in one or more parameters of pain or disability.[25] However, a recent analysis of the results of RCTs evaluating spinal manipulation for acute and chronic back pain reported that spinal manipulation was superior to sham therapies, but not superior to effective conventional treatments.[26] With the possible exception of back pain, chiropractic manipulation has not been shown to be efficacious for any condition.[27]

Acupuncture

Although acupuncture is among the oldest interventions for pain, it has remained a source of controversy among physicians not trained in this discipline, because there is no clear understanding of its physiological effects. Nonetheless, existing evidence indicates that it can be effective for pain, including chronic low back pain.[28]

Herbs and Nutritional Supplements

Patients with persistent pain are also turning to a wide variety of supplements, including chondroitin sulfate, glucosamine sulfate, S-adenosyl-methionine, vitamin B3 (niacinamide), methylsulfonylmethane, as well as various herbs such as cayenne, nettle, boswellia, autumn crocus and meadowsweet. These supplements are particularly popular with patients who have musculoskeletal pain. Only a few of these agents have undergone controlled clinical trials and rigorous studies are needed to establish therapeutic efficacy. Because many nutraceuticals interact with OTC and prescription drugs, knowledge of their use and effects is clinically important. Through its Web site, the FDA offers healthcare professionals (http://www.fda.gov/medwatch/report/hcp.htm) and consumers (http://www.fda.gov/medwatch/report/consumer/consumer.htm) the opportunity to report and review adverse events related to nutritional supplements (http://www.cfsan.fda.gov/~dms/supplmnt.html).

Interventional Approaches for Pain

There are many invasive modalities for persistent pain. They are typically categorized as injection therapies, neural blockade, and implant therapies. The most common injection therapies are trigger point injections for myofascial pain, joint injections for pain due to arthritis, and various spinal injections such as epidural steroid injections for back and neck pain. A recent systematic review[29]concluded there is moderate evidence that interlaminar epidurals can provide long-term relief from cervical pain and limited evidence for lumbar pain, moderate evidence for transforaminal epidural steroid in providing long-term relief for cervical or lumbar nerve root pain, and moderate evidence for caudal injections in providing long-term relief in chronic low back pain.

Neural blockade includes many techniques that can be used diagnostically or therapeutically. They may target somatic or sympathetic nerves. Although neurolytic blocks are now rarely performed, repeated blocks with local anesthetic can be a useful adjunct in the treatment of some conditions, such as reflex sympathetic dystrophy. Some pain specialists have the skills to undertake trials of spinal cord stimulation or neuraxial infusion. A successful trial can be followed by implantation of a generator or pump, respectively, for long-term therapy.

Pharmacologic Treatment of Persistent Pain

Pharmacologic interventions are an important component in the management of persistent pain and should be employed as part of the overall treatment plan. Before initiating pharmacotherapy, it is important to review the patient's medication history. A focused pain medication history should elicit as much information as possible about the previous use of analgesics and adjuvant agents, including information on dosage, duration of treatment, and adverse reactions. It is important to determine if past treatment failures were the result of an inadequate therapeutic trial of medication, inappropriate dosage adjustments, inadequate management of adverse reactions, and/or patient misconceptions of the goals of therapy. Patient (and caregiver) education is an important component of the treatment strategy.

Nonopioid analgesics, opioid analgesics, and a wide range of adjuvant analgesics are used in the pharmacologic management of persistent pain. Drug substitutions within a class should be considered before concluding that an entire class of agents is either ineffective or produces intolerable side effects. Selection of the most appropriate pharmacotherapy should take into account the patient's medical history and the pain characteristics. Given the controversial nature of long-term opioid therapy in persistent nonmalignant pain, it is better to view this approach as appropriate for some patients and inappropriate for others. As discussed in Module 2, clinicians must perform a comprehensive assessment, one goal of which may be to clarify the positioning of opioid therapy among the many other strategies that can be offered. This assessment must carefully consider whether the patient is likely to take his or her drugs responsibly. Individualizing treatment regimens is key to a successful outcome.

Nonopioid Analgesics

Acetaminophen and NSAIDs provide effective relief for many types of persistent pain. They are widely regarded as first-linetherapy for persistent joint or myofascial pain. In contrast to opioids, these drugs have a ceiling effect to analgesia; produce tolerance or physical dependence, are not associated with abuse or addiction, are antipyretic and (except for acetaminophen) anti-inflammatory. These drugs act by blocking prostaglandin formation.[30]

The nonopioid analgesics block the formation of prostaglandins through inhibition of the enzyme cyclooxygenase (COX).[31] COX has multiple isoforms. COX-1 is non-inducible and supports a range of physiologic functions, including gastric cytoprotection, renal blood flow, and platelet aggregation. In contrast, COX-2 is constitutive in some tissue but largely induced as part of the inflammatory cascade. An isoform known as COX-3 is in the brain and acts centrally as an analgesic-antipyretic. Acetaminophen blocks COX-3 and commercially-available NSAIDs block COX-1

and COX-2, with varying selectivity. The so-called selective COX-2 agents (now limited to celecoxib in the U.S. market) also inhibit COX-1 to some extent, but preferentially inhibit COX-2.

Current Use of Aspirin and Acetaminophen

With the advent of newer NSAIDs, the use of aspirin (acetylsalicylic acid) largely has been limited to cardioprotection for patients at risk of MI or stroke. It is uniquely effective for this indication because aspirin is the only irreversible inhibitor of platelet aggregation. Acetaminophen is similar to aspirin in its analgesic and antipyretic potency, but has no antiplatelet activity, little anti-inflammatory effect and does not damage the gastric mucosa. Acetaminophen is a common treatment of mild-to-moderate pain and is the recommended first-line analgesic therapy for the treatment of osteoarthritic pain. Historically, the maximum daily dose of acetaminophen for chronic use has been considered to be 4000 mg/day, and roughly half this dose in the setting of significant liver disease or heavy alcohol consumption. Given recent concern by the U.S. Food and Drug Administration (FDA) about unintentional overdose, it has been recommended that the conventional maximal safe dose be considered 2,600 mgs/day, instead of 4000 mgs/day. Significant liver disease or heavy drinking should be considered a relative contraindication to the use of acetaminophen. Patients should be warned about the risk of unintentional overdose and told to avoid combination products unless they are clear about the acetaminophen consumption.

Nonsteroidal Anti-inflammatory Drugs

All NSAIDs share the ability to inhibit the synthesis of prostaglandins through their inhibition of COX enzymes in peripheral tissues and in the central nervous system (see Table: Nonopioids Analgesics). There is little difference in the effectiveness of NSAIDs among different patient populations, but there are very large interindividual and intraindividual differences in the effectiveness and side effects produced by the various drugs. The failure of one NSAID does not predict failure of all NSAIDs. Combination therapy with two NSAIDs provides no known benefit because NSAID toxicity is additive.

The decision to try NSAID therapy requires a careful assessment of risk. The most common adverse events are gastrointestinal, including gastric and duodenal ulcers, upper and lower GI bleeding, gastritis, and dyspepsia. Because COX-1 is constitutive in the stomach and is involved in the production of gastroprotective prostaglandins, COX-1 inhibition is the primary factor in gastrointestinal (GI) adverse effects associated with NSAIDs. Nonselective NSAIDs increase the risk of GI erosion or bleeding more than the COX-2 selective coxibs, including celecoxib, and there also are differences among specific NSAIDs.[32,33] For example, the salicylate salts (*e.g.*, choline magnesium trisalicylate), naproxen, and ibuprofen also appear to have relatively lower risk of GI adverse reactions than other NSAIDs. A variety of factors predispose to the development of GI toxicity, most

Table: Systemic Pharmacotherapy With Nonpioid Drugs for Persistent Pain

Drug	Starting Dose	Usual Effective Dose (Maximum Dose)	Titration	Comments
Acetaminophen	325 mg q 4 h to 500 mg q 6 h	2 to 4 g/24 h (4 g/24 h)	After 4 to 6 doses	Reduce maximum dose 50% to 75% in patients with hepatic insufficiency; history of alcohol abuse
Choline magnesium salicylate	500 to 750 mg q 8 h	2000 to 3000 mg/24 h (same)	After 4 to 6 doses	Long half-life may allow qd or bid dosing after steady state is reached
Salsalate	500 to 750 mg q 12 h	1500 to 3000 mg/24 h (3000 mg/24 h	After 4 to 6 doses	In frail patients or those with diminished hepatic or renal function, it may be important to check salicylate levels during dose titration and after reaching steady state.
Celecoxib	100 mg bid or 200 qd	200 mg/24 h (400 mg/24 h)	After 2 to 3 days	Higher doses may be associated with a higher incidence of GI effects; patients with indications of cardioprotective ASA require aspirin-supplement

Adapted from The Medical Letters Handbook of Adverse Reactions Datacard.New Rochelle, NY: Medical Economics Company; 200147 and Allen LV, Berardi RR, Desimone EM, et al, eds. Handbook of Nonprescription Drugs.12th ed. Washington, DC: American Pharmaceutical

importantly advanced age and prior peptic ulcer disease or NSAID-induced gastroduodenopathy. Infection with Helicobacter pylori also is possibly a risk factor, but this is controversial.[34] Concurrent therapy with a H2 proton pump inhibitor, misoprostol, or in some studies, an H2 blocker, reduces the GI risk and is recommended in patients at relatively higher risk.[19]

NSAID Toxicity

All NSAIDs, including both the nonselective COX-1/COX-2 inhibitors and the selective COX-2 inhibitors, may contribute to renal toxicity. This is because the COX-2 enzyme is present in renal tissue and may be important in maintaining renal perfusion. The effect on kidney can lead to a variety of negative outcomes, including acute or chronic renal insufficiency, proteinuria, and fluid overload with edema.

An increased risk of cardiovascular toxicity related to prothrombotic effects (stroke/TIAs, myocardial infarction, symptomatic peripheral vascular diseases) has been established for both the nonselective COX-1/COX-2 inhibitors and the selective COX-2 inhibitors.[35,36] Although there is conflicting literature, the most prudent stance at the present time is that the risk exists with all NSAIDs and may be relatively higher among those that are more COX-2 selective; there appear to be important drug-selective differences, however, and there is evidence to suggest that the risk associated with naproxen is very low.[36] Although there remains much to learn about NSAID-induced prothrombotic effects, it is prudent to assume that the risk starts when dosing begins, is dose-dependent, and increases with the cumulative time receiving the drug. Presumably, patients with pre-existing atherosclerotic disease would be at increased risk, but the extent and clinical implications are as yet uncertain. It also is uncertain whether co-administration of low-dose aspirin would protect against this toxicity, and it must be noted that the co-administration of aspirin with celecoxib eliminates the advantage of the latter drug in terms of GI toxicity.

The cardiovascular toxicity associated with all NSAIDs may be determined or exacerbated by the effects of these drugs on blood pressure.[37] Over time, elevation of blood pressure could lead to an increased risk of cardiovascular events, as well as an increased risk of congestive heart failure. Blood pressure should be monitored in patients who receive these drugs.

Other Side Effects and Toxicity Risks

Other side effects associated with the NSAIDs include rashes, NSAID hypersensitivity and bronchospasm in patients with asthma and nasal polyps, blood dyscrasias (which are rare but can be fatal), liver abnormalities, and CNS effects, such as headache, drowsiness, and dizziness. Celecoxib is contraindicated in patients with sulfonamide allergy or sensitivity. As a class, NSAIDs may be associated with drug-drug interactions (see Table: Potential Drug Interactions with NSAID Analgesics).[38] An important pharmacodynamic interaction has been identified between specific NSAIDs, including ibuprofen and naproxen, and aspirin,[39] which leads to inhibition of aspirin's anti-aggregant effect on platelets. As a result, there is a theoretical concern that regular NSAID use may compromise the therapeutic effects of low-dose aspirin on the prevention of cerebrovascular and heart disease. The extent of this risk, in terms of cardiovascular events, is not known, but it is advisable to consider aspirin prophylaxis as another relative contraindication to the long-term use of an NSAID, and to perhaps avoid ibuprofen (the best studied and clearest offender) if aspirin-treated patients would benefit from an NSAID; it also is reasonable to tell patients to take their daily dose of aspirin several hours before their daily dose of the NSAID on the assumption that the interaction would have the least impact with this timing.

Concern about the risk associated with long-term NSAID therapy should be relatively high in patients with factors that predispose to GI toxicity or cardiovascular toxicity, or who have renal insufficiency or a bleeding diathesis. If the decision is made to use an NSAID, it is reasonable to consider a COX-2 selective drug in those predisposed to GI toxicity, or to consider coadministration of a gastroprotective agent, specifically a proton pump inhibitor or misoprostol. In those predisposed to atherothrombotic cardiovascular toxicity, it may be reasonable to consider naproxen. In all cases, it is reasonable to consider choosing NSAIDs with relatively good safety profiles, such as celecoxib, naproxen or naproxen sodium, or ibuprofen, ketoprofen, diclofenac, etodolac, nabumetome, meloxicam, or one of the nonacetylated salicylates.

Opioid Analgesics

Despite concerns and controversies over misuse, addiction, tolerance, adverse effects, and regulatory action, expert opinion supports opioid therapy for many persistent pain conditions. The American Pain Society (APS), the American Academy of Pain Medicine (AAPM), and the American Society of Addiction Medicine (ASAM) all advocate cautious use of opioid analgesics for carefully selected and closely monitored patients with persistent nonmalignant pain.[40,41] Opioid analgesics are conventionally considered the first-line therapy for severe acute pain and moderate to severe persistent pain due to cancer, AIDS, and other advanced illnesses. The role of long-term opioid therapy for persistent nonmalignant pain continues to be controversial, but it is reasonable to consider these drugs in all patients with moderate to severe persistent pain only after carefully weighing the answers to the following questions:

- What is conventional therapy for the pain syndrome in question?
- Are there other therapies with as good, or better, therapeutic indices than opioids?
- Is this patient at relatively high risk of opioid adverse effects?
- Is this patient likely to be a responsible drug-taker over time?

Table: Nonopioid Analgesics

Drug Name	Usual Adult Dose	Max. Adult Dose
Acetaminophen (Anacin Aspirin Free, Genepap, Genebs, Tylenol, and others)	650-1000 mg PO q 4-6 hrs	2,600 - 4000 mg
Salicylates		
• aspirin (Bayer, Ecotrin, Genecote, Norwich Aspirin)	650-975 mg PO q 4-6 hrs	4000 mg
• choline magnesium trisalicylate* (Tricosol, Trilisate)	1000-1500 mg PO q 12 hrs	3000 mg
• diflunisal* (Dolobid, Diflunisal Tablets)	1000 mg PO initial dose followed by 500 mg q 12 hrs	1500 mg
• magnesium salicylate* (Doan's Caplets, Keygesic-10, Momentum, Mobidin)	650 mg PO q 4-6 hrs	
• salsalate (Argesic SA, Disalcid, Salflex, Salsitab, Mono Gesic)	1000-1500 mg PO q 12 hrs	3000 mg
• sodium salicylate*	325-650 mg PO q 3-4 hrs	
Other NSAIDs		
• sulindac* (Clinoril)	200 mg PO q 12 hrs, after satisfactory response is achieved, dose may be decreased accordingly	400 mg
• diclofenac potassium* (Cataflam)	50 mg PO q 8 hr	150 mg
• etodolac* (Lodine, Etodolac Extended-Release)	200-400 mg PO q 6-8 hr	1200 mg
• fenoprofen calcium* (Nalfon)	200-600 mg PO q 6 hrs	2400 mg
• ibuprofen* (Advil, Genpril, Haltran, Ibu-Tab, IBU, Menadol, Motrin)	400-800 mg PO q 6-8 hrs	3200 mg
• indomethacin* (Indocin)	25-50 mg PO q 8 hrs	150 mg
• ketoprofen* (Actron, Ketoprofen Capsules, Orudis, Orudis KT, Oruvail)	25-50 mg PO q 6-8 hrs	300 mg
• ketorolac tromethamine* (Ketorolac Tromethamine, Toradol)	Pts.<65 yrs of age: 30-60 mg IM initially followed by 15-30 mg q 6 hrs. Oral dose following IM dosage: 10 mg q 6-8 hrs. IV Dosage: 30 mg IV q 6 hrs Pts.>65 yrs of age: 15 mg IV/IM q 6 hrs	Pts.<65 yrs of age: 120 mg Pts>65 yrs of age:60 mg
• meclofenamate sodium* (Meclomen)	50-100 mg PO 4-6 hrs	400 mg
• mefenamic acid* (Ponstel)	500 mg PO initially followed by 250 mg PO q 6 hr	1250 mg
• meloxicam* (Mobic)	7.5 mg PO initially once dailymay increase by 7.5 mg	15 mg
• nabumetone* (Relafen)	1000 mg PO initially once daily may increase BID to 1500-2000 mg	2000 mg
• naproxen* (Naprosyn, EC-Naprosyn)	500 mg PO initially followed by 250 mg PO q 6-8 hrs	1250 mg the first day, then 1000 mg
• naproxen sodium* (Anaprox, Aleve, Naprelan)	550 mg PO initially, followed by 275 mg PO q 6-8 hrs	1375 mg the first day, then 1100 mg
Coxibs		
• celecoxib (Celebrex)	100-200 mg PO q 12 hr	400 mg

Modified from Institute for Clinical Improvements, October 2002. *Available by nonproprietary name.

Table: Potential Drug Interactions with NSAID Analgesics

Drug Combination	Effect	Management Options/Considerations
Oral anticoagulants with all NSAIDs	Increased oral warfarin activity Increased risk of bleeding (especially GI)	Monitor prothrombin time and for occult blood in stool and urine Avoid concurrent use of aspirin
Lithium with all NSAIDs	Increased steady state lithium concentration Lithium toxicity	Monitor lithium concentrations carefully Interactions less likely with aspirin than naproxen sodium or ibuprofen
Antihypertensive agents (beta-blockers, ACE inhibitors, vasodilators, diuretics) with several NSAIDs	Antihypertensive effect antagonized Hyperkalemia may occur with potassium-sparing diuretics and ACE inhibitors	Monitor blood pressure and cardiac function Monitor potassium concentration Low-dose aspirin (e.g., 75 mg/day) may not interact with ACE inhibitor
Digoxin with NSAIDs	Renal clearance inhibited	Monitor digoxin concentrations Adjust dose as necessary
Valproate with aspirin	Oxidation of valproate inhibited Up to 30% reduction in clearance Possible valproate toxicity	Avoid aspirin with valproate Naproxen sodium is an alternative
Phenytoin with ibuprofen and high-dose salicylates	Increased phenytoin levels: phenytoin is displaced from serum protein binding sites, if phenytoin metabolism is saturated or folate concentrations are low	Monitor unbound phenytoin concentrations and adjust dose, if necessary Ensure patient has sufficient folate intake
Methotrexate with all NSAIDs	Reduced renal clearance Increased plasma methotrexate concentration	Avoid NSAIDs with high-dose methotrexate Monitor concentrations with concurrent therapy
Antacids (in high doses) with salicylates, aluminum hydroxide,and naproxen sodium	Salicylate concentrations possibly reduced by 25% Aluminum hydroxide decreases naproxen sodium absorption	Monitor clinical status Determine if salicylate dose needs to be increased
Probenecid with naproxen sodium	Reduced clearance of naproxen sodium	Monitor for adverse effects
H_2-blocking agents with salicylates, naproxen sodium	Potential salicylate toxicity Potentially reduced naproxen sodium effect	Monitor salicylate concentration Monitor clinical status
Corticosteroids with aspirin; salicylates (high doses	Possible decreased salicylate effect due to increased clearance	Monitor salicylate concentration when changing corticosteroid dose
Insulin with salicylates	Possible decreased hypoglycemic effect with large salicylate doses	Monitor blood glucose
Sulfonylureas with salicylates (moderate to high-dose)	Hypoglycemic activity increased	Avoid concurrent use Monitor blood glucose concentrations when changing salicylate dose
Cephalosporins with aspirin	Possible increased bleeding risk	Avoid concurrent use
Aminoglycoside antibiotic sand NSAIDs	Inhibits aminoglycoside renal clearance	Monitor antibiotic concentrations and adjust dose as needed

Source: The Medical Letters Handbook of Adverse Reactions Datacard.New Rochelle, NY: Medical Economics Company; 200147 and Allen LV, Berardi RR, Desimone EM, et al, eds. Handbook of Nonprescription Drugs. 12th ed. Washington, DC: American Pharmaceutical Association; 2000.

If a persistent pain has not responded to other conventional treatments with equal or better therapeutic indices, then a trial of opioid therapy with the intention of transitioning to long-term care should be considered. The goals of this treatment should be both diminished pain severity and improved quality-of-life, ideally accompanied by improvements in physical, psychological, social and occupational functioning. For many patients with persistent pain, long-term opioid therapy may provide the only means of achieving a functional lifestyle.

Long-Term Opioid Therapy

Long-term opioid therapy does not preclude the concurrent use of other treatments (*e.g.*, nonopioid analgesics, CBT, physical/rehabilitative therapies). Safe and effective prescribing of opioids on a long-term basis requires skills in both opioid pharmacotherapy and risk assessment and management.[41,42] Guidelines are discussed in modules 2 and 4. Useful recommendations to guide long-term opioid therapy in persistent pain have been developed by the Federation of State Medical Boards (FSMB); these recommendations are summarized in the Table. A sample agreement that can be used as an educational tool for patients, and to set the expectations for therapeutic adherence, has been developed by the AAPM.[43] This type of document may be a useful tool, particularly for educating patients about appropriate expectations for the therapy.

FSMB Recommendations for the Use of Controlled Subtsances

- Review pertinent data
- Adequate history and physical exam
- Clinical impression
- Individualized treatment plan
- Informed consent
- Re-evaluation & follow-up
- Consultations as appropriate
- Accurate, complete medical records
- Compliance with DEA & state agencies

Model Guidelines for the Use of Controlled Substances for the Treatment of Pain. The Federation of State Medical Boards of the United States, Inc. Available at www.fsmb.org.

Classifications of Opioid Analgesics

Most of the opioids used in clinical practice are full agonists (Table: Opioid Analgesic — Classicification by Receptor Activity). Partial agonists (*e.g.*, buprenorphine) have lower intrinsic activity at the mu opioid receptor and the mixed agonist-antagonists (*e.g.*, butorphanol, nalbuphine or dezocine) have different effects at the various opioid receptors. The latter drugs have a ceiling effect for analgesia and at least some nonanalgesic effects compared with full agonists.

Opioid agonist drugs may be further divided into short-acting and long-acting, based on their time-action properties. For example, morphine is a short-acting opioid and, as such, requires frequent dosing to maintain analgesia. Extended-release oral (*e.g.*, morphine, oxycodone, oxymorphone) and transdermal (*e.g.*, fentanyl) formulations, and oral opioids with long half-lives (e.g., methadone, levorphanol) are alternatives to short-acting opioids, and are preferred for the management of persistent pain. Tramadol and a new drug on the market, tapentadol, are centrally-acting analgesics that have mu opioid actions and also inhibit the reuptake of monoamines such as norepinephrine and serotonin reuptake. Tramadol usually is considered for moderate-to-severe pain. Dose escalation to treat persistent severe pain may be precluded by dose-related toxicity; doses greater than 400 mg/d are associated with an increased risk of seizures.

Even if a patient has been receiving a short-acting opioid for a time, the decision to implement open-ended long-term opioid therapy should begin with a trial. The patient should understand that a trial that is not successful will be stopped. At no time does the pharmacology of the opioid drugs preclude dose tapering and discontinuation of therapy if an analysis of benefit and burden suggests that the approach is not sufficiently effective or safe to justify ongoing administration.

When initiating a trial of an opioid for persistent pain in opioid-naïve patients who can use oral medications, the usual opioids selected include tramadol (or, presumably, tapentadol) or one of a group of full agonist drugs conventionally selected for pain of this type. These drugs include codeine, hydrocodone and oxycodone, which in this context (patients who are relatively opioid-naïve) usually are selected in a formulation combined with acetaminophen, aspirin or ibuprofen. Full mu agonists that may be administered as a single entity oral or transdermal formulation, including morphine, hydromorphone, oxycodone, oxymorphone, methadone, levorphanol, and fentanyl, do not exhibit a ceiling effect with increasing dose or carry the limitation in dosing imposed by the nonopioid constituent. In practice, the “ceiling” for these single entity drugs relates only to the occurrence of opioid-related side effects as the dose is increased. Most patients experience satisfactory analgesia before this treatment-limiting toxicity occurs.

Selecting an Opioid Analgesic

Codeine is a commonly used mu agonist, but is the only opioid that is a pro-drug, which must be converted to morphine in the body through action at the 2D6 isozyme of the hepatic CYP440 complex in the liver. Five to ten percent of the population are slow metabolizers, potentially unable to synthesize enough morphine from codeine to produce analgesia. To avoid this concern, another opioid, one containing oxycodone, hydrocodone, tramadol or another drug, can be used. Other opioids that generally should not be used for long-term therapy include meperidine (Demerol,

Table: Opioid Analgesics

Agent	Indications	Dosing Interval	Routes of Administration/ Dosage Forms	Comment*
morphine**	Severe acute pain (trauma, post-operative, MI) or persistent pain	Varies with IR and CR	PO (IR and CR),PR,IV, SC,EA,IA,SL	Metabolite can accumulate in setting of RF Used as a standard of comparison for all opioid drugs; can stimulate histamine release
hydromorphone (Dilaudid)	PO: pain management when opioid therapy is appropriate Parenteral: moderate to severe pain (trauma,MI, surgery, burns, renal colic, biliary colic, cancer)	Varies by route	PO,PR,IV,SC, EA,IA	Useful alternative to morphine Available as high-potency injectable that facilitates SC administration Not available in controlled-release preparation 5 to 7 times more potent than morphine, with a shorter half-life than morphine
fentanyl	Transdermal: persistent pain Oral transmuscosal: breakthrough pain Parenteral: acute severe pain	Varies with ROA and form 72 h for TD	IV,EA,IA,TD, OTFC	Although 1:1 ratio with morphine was in single dose study, there is a change with chronic dosing and large dose reduction (75% to 90%) is needed when switching to methadone.
oxycodone (OxyContin)**	Moderate to moderately severe pain (trauma, postoperative pain, musculoskeletal disorders, abdominal pain,dental pain,cancer pain) CR for moderate to severe pain if opioid is required for extended time	Varies with IR and CR	PO (IR and CR)	TD fentanyl contraindicated for opioid- naive patients,acute pain, post-operative pain,mild or intermittent pain responsive to PRN or nonopioid therapy, and at doses above 25 mcg/h at the initiation of opioid therapy TD fentanyl should not be used in children <12 y or patients <18 y who weigh <110 lb.,except in monitored settings TD and oral transmucosal formulations available, including OTFC (fentanyl in sweetened matrix) IV fentanyl often combined with benzodiazepines for procedural analgesia and sedation TD fentanyl long acting, can control pain for up to 72 h but a few patients may require q 48-hour dosing Patients must follow correct patch application procedure for TD fentanyl and avoid directly exposing application site to heat
oxymorphone (Opana)**	Moderate to severe acute pain (trauma, postoperative pain, musculoskeletal disorders, abdominal, dental, cancer pain) CR for moderate to severe pain if opioid required for extended time	Varies with IR and CR IV	PO (IR and CR)	For CR, 5 mg is the recommended starting dose in opioid naïve patients
meperidine (Demerol)**	Moderate to severe pain (migraine, trauma, postoperative, acute abdominal pain)	3-4 h	PO, IV, SC, EA, IA	High doses may cause agitation, muscle fasciculations, seizures, or hypotension Use carefully in patients with renal insufficiency, seizure disorders, and cardiac arrhythmia NR for persistent pain due to accumulation of toxic metabolite that may cause CNS excitement, and seizures Potential for metabolite accumulation suggests duration of use less than 48 hours or 600 mg in 24 hours Oral administration NR for severe pain

Table: Opioid Analgesics (continued)

Agent	Indications	Dosing Interval	Routes of Administration/ Dosage Forms	Comment*
morphine**	Severe acute pain (trauma, post-operative, MI) or persistent pain	Varies with IR and CR	PO (IR and CR),PR,IV, SC,EA,IA,SL	Metabolite can accumulate in setting of RF Used as a standard of comparison for all opioid drugs; can stimulate histamine release
hydromorphone (Dilaudid)	PO: pain management when opioid therapy is appropriate Parenteral: moderate to severe pain (trauma,MI, surgery, burns, renal colic, biliary colic, cancer)	Varies by route	PO,PR,IV,SC, EA,IA	Useful alternative to morphine Available as high-potency injectable that facilitates SC administration Not available in controlled-release preparation 5 to 7 times more potent than morphine, with a shorter half-life than morphine
fentanyl	Transdermal: persistent pain Oral transmuscosal: breakthrough pain Parenteral: acute severe pain	Varies with ROA and form 72 h for TD	IV,EA,IA,TD, OTFC	Although 1:1 ratio with morphine was in single dose study, there is a change with chronic dosing and large dose reduction (75% to 90%) is needed when switching to methadone.

*In addition to any side effects listed, all drugs have mu agonist class side effects, precautions, warnings, and contraindications.
**Controlled-release (CR) tablets are taken whole and must not be broken, chewed or crushed to prevent potential toxic dosage

Legend: CNCP,chronic noncancer pain; CNS,central nervous system; CR,controlled-release; EA,epidural analgesia; IA,intrathecal analgesia; IM,intramuscular; IR,immediate release;IV,intravenous; MI,myocardial infarction;NR,not recommended; NSAID,nonsteroidal anti-inflammatory drug; OA,osteoarthritis; OTFC,oral transmucosal fentanyl citrate;PO,per os (oral); PR,rectal; PRN,as needed; RA,rheumatoid arthritis; RF,renal failure; ROA,route of administration; SC,subcutaneous; SL,sublingual; TD,transdermal.

Modified with permission from Berry PH, Chapman CR, Covington EC, et al. Pain: Current Understanding of Assessment, Management, and Treatments. Reston, VA: National Pharmaceutical Council and the Joint Commission on Accreditation of Healthcare Organizations; December, 2001. Appendix: Opioid Analgesics 406140M1 12/11/03 11:21 PM Page 40.

others) and propoxyphene, both of which have active metabolites that are associated with tremulousness, delirium and seizures.

Initial oral dosing regimens typically utilize a short-acting preparation, and the dose is titrated upward to determine the optimal dosage. Patients prescribed short-acting drugs may require multiple doses throughout the day, which can be inconvenient and reduce adherence. If pain is constant or recurs frequently, opioids should be administered on a time-contingent (regularly scheduled) basis and this is usually best accomplished with a long-acting opioid.

Selecting a Long Acting Opioid Analgesic

Once the total dose of an immediate-release formulation is determined, the regimen can be converted to an equivalent daily milligram dose of a modified-release formulation. Modified-release preparations of morphine increase the drug's duration from 2 to 4 hours (for short-acting agents) to 8 to 12 hour for some formulations and 24 hours for others. Modified-release formulations are also available for oxycodone (oral), oxymorphone (oral), and fentanyl (transdermal); modified-release forms of other opioids are under investigation.

Methadone is a long-acting opioid that typically can be prescribed three to four times per day. It is the least costly of the pure mu agonist drugs. These attractive features are balanced by the reality that there are risks in using methadone for pain that exceed other pure mu agonist drugs.[41,42] First, when methadone is substituted for another opioid, its potency is difficult to predict. It may be more potent than anticipated, and its potency increases when the substitution occurs in the context of high-dose therapy. Accordingly, when switching to methadone, the calculated equianalgesic dose must be reduced far more than would be routine for other drugs.[44] Second, although methadone has a half-life of 24 hours in most patients, the half-life can vary from 12 hours to 150 hours. Accordingly, patients must be monitored for a relatively long time to ensure that steady state levels have been reached. Without careful monitoring, there is a risk of "overshooting" to toxicity as the plasma concentration continues to slowly rise toward steady state after dosing is initiated or the dose is increased. Third, methadone has been shown to prolong the QTc, adding some risk to the use of this drug.[45] Given these considerations, methadone should be used only by clinicians who are knowledgeable about its pharmacology and the dosing strategies that must be used to ensure safety.

Risk Management with Opioid Analgesics

The safe and effective prescribing of opioid medication requires BOTH skills in the methods to optimize the pharmacologic outcomes and skills in risk assessment and management. The risks of opioids relate both to side effects and to the potential for abuse, addiction and diversion that are inherent in drugs of abuse.

Recent studies have evaluated numerous factors as potential predictors of problematic drug-related behavior, including abuse and addiction. The most consistent are a prior or current history of alcohol or drug abuse, a family history of alcohol or drug abuse, and a history of major psychiatric disorder.[46,47] By assessing, at minimum, these characteristics, the clinician should be able to stratify risk. The presence of one or more of these factors should indicate that the patient may be at relatively high risk of problematic drug use, an important consideration in the decision to proceed with therapy, and if this is done, in the decisions that must be made about the degree of structure and control that should be incorporated.

Table: Opioid Analgesic — Classicification by Receptor Activity

Opioid type	Medications	Notes
Pure agonists	Codeine Hydrocodone Dihydrocodeine Morphine Hydromorphone Fentanyl Oxycodone Oxymorphone Levorphanol Methadone Meperidine Propoxyphene	No clinically relevant ceiling effect to analgesia; as dose is raised, analgesic effects increase until analgesia is achieved or dose-limiting side effects supervene. Codeine, hydrocodone, oxycodone combination products are most widely prescribed and used for short-term and long-term management of moderate to severe pain. Codeine not preferred because of variation in metabolic conversion to active metabolite. Dosing of combination products limited by safety of the nonopioid constituent. Single entity formulations, particularly long-acting versions, are mainstay of therapy for long-term moderate to severe cancer pain. Meperidine and propoxyphene are not preferred due to potential effects of toxic metabolites. Methadone must be used with caution; only clinicians who are knowledgeable about the risks posed by long and variable half-life, unpredictable potency, and potential for QTc prolongation should use this drug without guidance.
Agonist-antagonists	***Partial agonists*** Buprenorphine ***Mixed agonist-antagonists*** Butorphanol Dezocine Nalbuphine Pentazocine	Agonist-antagonists include μ-agonists with lower intrinsic efficacy (partial agonists) and drugs that have agonist effects at one receptor and antagonist effects at another (mixed agonist-antagonists). Most developed to be less attractive to those with addiction. All have a ceiling effect for analgesia. All have the potential to cause withdrawal in patients with physical dependency to agonist opioids. Some, most notably pentazocine and butorphanol, have relatively high risk of psychotomimetic side effects. Buprenorphine available in some countries as a transdermal patch and is a useful analgesic.

Table: Recommendations to Guide Long-term Opioid Therapy in Persistent Pain

- A comprehensive evaluation of the patient's physical and psychosocial status should precede the prescription of long-term opioid therapy. This assessment should review the following:
  - —history of present illness (pain characteristics, prior therapies and evaluations, impact of pain on overall function);
  - —medical and psychiatric comorbidities, including any substance abuse and/or addiction; and
  - —social aspects and family history (family and peer influences on pain, support ne works, drug use by family members or social contacts).
- Opioid therapy can be appropriate for patients with persistent moderate to severe pain when:
  - —data suggest opioids are likely to be effective;
  - —opioids have an equal or better therapeutic index than alternative therapies;
  - —the medical risk of opioid therapy is relatively low;
  - —the patient is likely to be responsible in using the drug; and
  - —opioid therapy is considered part of the conventional management for the pain syndrome.
- A history of substance abuse or prior prescription drug misuse, severe character pathology and/or a chaotic home environment should be viewed as relative contraindications to prescribing opioid drugs.
- One clinician should take primary responsibility for the patient's pain management. At the initiation of care, this clinician should review the patient's complete medical record and then review all medications at each patient visit.
- Patients should give informed consent before the start of opioid therapy and the consent discussion should be documented in the medical record. This discussion should include the low risk of opioid addiction in patients under a physician's care, the necessity of adherence to prescribed dosing, the potential for cognitive impairment when taking the drug alone and/or in combination with sedative/hypnotics and the likelihood that physical dependence will occur.
- After selecting a medication, follow-up visits should be scheduled as appropriate and consistent with any perceived risk of aberrant medication use and abuse. Patients assessed to have low risk can be provided with detailed instructions for dosing and return for follow-up within 2-4 weeks. In patients assessed to have high risk of aberrant drug use, several strategies can be used, including a written agreement about therapy, frequent follow-up visits, urine drug screens, pill counts at visits and co-management with an addiction medicine specialist.
- The dose and dosing frequency should optimize the patient's pain relief. Therapeutic drug levels should be achieved; around-the-clock; long-acting opioid drugs are preferred; and the decision to co-administer a short-acting opioid for breakthrough pain should be made on a case-by-case basis.
- Typically, initial dose titration requires several weeks and improvements in physical and social function, as well as incremental pain relief, should be emphasized; patients should be educated to expect partial analgesia as the likely outcome of therapy.
- Failure to achieve at least partial analgesia at relatively low initial doses in a patient with no substantial prior opioid exposure raises questions about the potential treatability of the pain syndrome with opioids; such an occurrence should lead to reassessment of the pain syndrome.
- Analgesic gains with opioid therapy should be used to encourage improved physical and social functioning; instituting or re-instituting therapies to these ends should be considered.
- Some patients may be permitted access to additional analgesic on days of increased pain. Breakthrough pain can be treated with a short-acting agent, or, patients may be instructed to take one or two extra doses of their usual opioid medication on the day they experience breakthrough pain. When allowed extra doses for breakthrough pain, some patients should be advised to make an equal reduction in dose on the subsequent day.
- After initial dose titration, most patients should be seen at least monthly, and their prescription revised or renewed at each visit. When the patient achieves adequate pain control and appropriate medication use has been demonstrated, less frequent visits may be acceptable.
- Exacerbations of pain may occur and, following a careful assessment, the clinician may decide to increase the usual/maintenance dose. This change in therapy should be explained clearly and documented in the medical record. If repeated dose escalation is needed to maintain pain control, the clinician should reevaluate the pain syndrome and the patient.
- Evidence of aberrant drug-related behaviors must be carefully assessed. In some cases, tapering and discontinuation of opioid therapy will be necessary. Other patients may appropriately continue therapy if the structure for monitoring is tightened. Consideration should be given to consultation with an addiction medicine specialist and/or a pain specialist.
- At each patient visit, the assessment should specifically address the 4A's (with clear documentation in the patient's medical record). These outcomes are:
  - —comfort (Analgesia);
  - —opioid-related side effects (Adverse effects);
  - —physical and psychosocial functioning (Activities of daily living);
  - —and drug-related behavior (Aberrant drug-related behavior).
- If any of these outcomes is not consistent with the goals of the therapy, an intervention should be planned and also documented: Use of pain diaries or pain severity assessment instruments may be helpful, but should not be required.

To convert one opioid into another:

Step 1: Calculate the average total daily dose of the current opioid medication.

Step 2: Divide by the equianalgesic dose (ED) of the current opioid in the chart to get the EDU.

$$\frac{\text{Total dose of Opioid A}}{\text{ED Opioid A}} = \text{EDU}$$

Step 3: Multiply the EDU by the ED for the new drug to get the total daily dose of the new opioid.

Formula: Total dose of Opioid A / ED Opioid A X ED Opioid B = Total Dose Opioid B

Reproduced with permission from Kaniecki, R. Headache assessment and management. *JAMA.* 2003;289; 1430-1433.

Some patients need no special monitoring and others need extensive structure to assist them in adhering to the pain management therapy and to increase the likelihood that any problems are identified promptly. The latter structure may include frequent visits, prescription of small amounts of opioids, use of an opioid agreement (describing expectations and consequences of problematic behavior), occasional urine drug screens, the requirement of consultations or co-therapy with mental health care providers, and other similar strategies. Clinicians who cannot establish structured approaches should not independently treat patients who require such an approach.

Dosing

To optimize pharmacological outcomes during opioid therapy, the dose must be individualized through the process of gradual dose titration. Full mu opioid agonists, such as morphine, have a fairly linear dose response curve and upward dose titration can be done until either satisfactory analgesia is reported or the patient experiences an intolerable and unmanageable side effect. The latter scenario is known as "poor responsiveness" and should be considered specific for the particular opioid and route of administration.

One approach for managing a patient with pain that is poorly responsive to an opioid regimen is to switch to an alternative opioid. So-called opioid rotation—changing from one opioid to another in an effort to identify the most effective drug—is conventional practice justified by the large intra-individual differences in the response to the various opioids. Given the differences in potencies and other sources of variation, a switch from one opioid to another must be performed using an equianalgesic dose table (Table: Equianalgesic Dosing of Opioid Analgesics).[44] The recommended approach[44] involves two steps: First, the dose of the new opioid that is equianalgesic to the total opioid consumed on average during the past several days is calculated from the equianalgesic dose table. This calculated dose is reduced by 25%-50%, with two exceptions: the dose of methadone is reduced by 75%-90% and the dose of transdermal fentanyl is not reduced at all. Second, this automatic dose reduction is followed by a second dose adjustment based on a clinical assessment of the severity of the pain and the medical frailty of the patient; in this adjustment, the newly calculated dose of the opioid can be increased or decreased by 15%-20%.

Table: Equianalgesic Dosing of Opioid Analgesics*

Oral/Rectal Dose (mg)	Analgesic	Parenteral Dose SC, IM, IV(mg)
30	morphine	10
20	oxycodone	NA
4	levorphanol	2
7.5	hydromorphone	1.5
NA	fentanyl	0.2
30	hydrocodone	NA
20	methadone	10
200	codeine	120
300	meperidine	100

*An equianalgesic table can be used to switch drugs or routes of administration. Adapted from The Education for Physician's on End-of-Life Care (EPEC) Curriculum. Chicago: Robert Wood Johnson Foundation, 1999413 and Foley KM. The treatment of cancer pain. *N Engl J Med.* 1985;313:84-95.

Once an opioid regimen is begun, dose titration usually is needed and should be accomplished by increasing the dose as a percentage of the total daily dose. An increase of 25% to 50% typically is safe. Thus, a patient with inadequate pain relief with 30 mg morphine can receive 45 mg, while a patient on a dosage of 300 mg may require an increase to 450 mg with careful monitoring of the patient for side effects. Frequent reassessment is invaluable in ensuring appropriate and adequate dosing. While the occurrence of tolerance to the analgesic effects of opioid drugs can occur, and is a common worry of clinicians and patients alike, numerous surveys have demonstrated that most patients can be maintained

Table: Initiating Opioid Analgesics for Persistent Nonmalignant Pain Conditions

Drug	Starting Dose	Titration	Comment
Hydrocodone	5 mg q 4 to 6 h	After 4 to 6 doses	Only available in combination. Useful for acute recurrent, episodic, or breakthrough pain; daily dose limited by fixed-dose combinations with acetaminophen or NSAIDs.
Hydromorphone	2 mg q 3 to 4 h	After 3 to 4 doses	For breakthrough pain or for around-the-clock dosing. In patients with renal impairment or in the elderly, hydromorphone is usually well tolerated with less somnolence and cognitive impairment than morphine.
Levorphanol	2 mg q 6 h until steady state reached and then q 8 h	--	Levorphanol is a relatively long-acting opioid and often can be dosed q 8 hours after it reaches steady state which occurs after ~2 days. The pharmacokinetics of levorphanol have not been well studied.
Methadone	5 mg q 4 h until steady state is reached and then q 8 h to 12h	--	Relatively long duration of action ~4 to 8 hrs. Although the pharmacokinetics of methadone are complex, it can be safely used for pain when initiated in a low dose and titrated to patient response. **When switching or rotating from one opioid to methadone, a dose reduction of 75% to 95% of the expected equianalgesic dose of methadone is required due to incomplete cross tolerance.**
Morphine, immediate-release	5 to 10 mg q 4 h	After 1 to 2 doses	Recommended for breakthrough pain. Oral liquid concentrate is available. Metabolite can accumulate in setting of renal failure.
Morphine, modified-release	15 mg q 12 h	After 2 to 3 days	Usually started after initial dose determined by effects of immediate-release opioid; toxic metabolites of morphine may limit usefulness in patients with renal insufficiency or when high-dose therapy is required; controlled-release formulations may require more frequent dosing if end-of-dose failure occurs regularly. **Tablets should not be broken, crushed, or chewed as rapid release and absorption may lead to a potentially toxic dose.**
Oxycodone, immediate-release	10 mg qd	20 mg/24 h (40 mg/24 h)	Useful for acute recurrent, episodic, or breakthrough pain; dose limited by fixed-dose combinations with acetaminophen or NSAIDs. **Care needs to be taken to avoid toxicity with acetaminophen combinations.**
Oxycodone, modified-release	10 mg q 12 h	10 mg q 12 h	Usually started after initial dose determined by effects ofimmediate-release opioid. The 80 and 160 mg tablets are used in opioid-tolerant patients only. **Tablets should not be broken, crushed, or chewed as rapid release and absorption may lead to a potentially fatal dose.**
Oxymorphone, immediate-release	5-10 mg q 4 - q 6h	See comments	Titrate to acceptable pain relief
Oxymorphone, modified-release	5-10 mg q 12h	After 3 to 7 days	Older patients have plasma levels 40% higher than younger patients. Start with the lowest does and proceed cautiously with dose titration. **Tablets should not be broken, crushed, or chewed, as rapid release and absorbtion may lead to a potentially fatal dose.**
Transdermal fentanyl	25 mcg/h patch q 72 h	After 3 days	Usually started after initial dose determined by effects of immediate-release opioid; currently available lowest dose patch (25 mcg/h) recommended for patients who require 60 mg per 24 hour oral morphine equivalents; peak effects 18 to 24 hours. Duration of effect is usually 3 days, but may range from 48 h to 96 h. Fever has been reported to increase absorption, producing somnolence in some patients. Many opioid-naïve elderly patients cannot tolerate the 25 mcg patch.
Tramadol	25 mg q 4 to 6 h	After 4 to 6 doses	Mixed opioid and central neurotransmitter mechanism of action; monitor for opioid side effects, including drowsiness and nausea.

Source: The Management of Persistent Pain in Older Persons. J Am Geriatr Soc. 2002;50:S205-S224.

on a stable dose of opioids for prolonged periods. Some require no dose escalation to retain analgesic effects; others require periodic dose changes that can be accommodated by the clinician and patient. Given this observation, increased pain should trigger evaluation of disease progression before concluding that tolerance is the cause. Tolerance does develop within days to weeks for most of the common adverse effects of opioids; tolerance appears to develop more slowly and less completely for constipation and many patients, particularly those with other concurrent causes of constipation, never report a reduction in this side effect.

The co-administration of a an immediate-release, short-acting "rescue" dose for breakthrough pain is now the standard approach when treating persistent pain in the cancer population, but in the population with opioid-treated noncancer pain, the rescue dose should not be considered the standard of care; patients should be carefully assessed to determine whether the potential benefits of this additional opioid outweigh any risks. A typical rescue dose consists of 5% to 15% of the patient's 24-hour dose of medication or the equivalent dose of a different drug, as calculated from analgesic conversion charts (Table: Equianalgesic Dosing of Opioid Analgesics). The only exception to this is provided by the so-called rapid onset fentanyl formulations, such as oral transmucosal fentanyl citrate or fentanyl buccal tablets, both of which should be initiated at relatively low doses (*e.g.*, 200 mcg or 100 mcg, respectively) in all patients, and then titrated upward as needed.

Opioid Analgesics: Adverse Reactions

Constipation

Side effects are common during opioid therapy and should be anticipated and treated (see Table: Strategies to Minimize Opioid Side Effects). Constipation is the most common side effect of opioids during chronic use, and is a consequence of both central nervous system effects and binding to opioid receptors in the GI tract. Unfortunately, patients often do not develop tolerance to this troublesome side effect. A routine prophylactic bowel regimen should be considered in patients who are predisposed to this side effect, such as the elderly, sedentary patients, patients with poor oral intake, and patients treated with other constipating drugs. Methylnaltrexone, an injectable opioid antagonist that does not cross the blood-brain barrier, was recently approved in the United States for refractory opioid-induced constipation. Occasionally patients are offered oral naloxone, which has very poor oral bioavailability and also has been used to treat opioid-induced constipation.

Strategies to Minimize Opioid Side Effects

- Preventive measures
- Slow titration of doses
- Verifying that symptoms are an opioid side effect
- Changing the dosing regimen or route of administration
- Using a nonopioid or adjuvant analgesic for an opioid sparing effect
- Adding a drug to counteract the side effect
- Constipation prophylaxis

Sedation

Opioid-induced sedation, mental clouding and impaired psychomotor function occur in a dose-dependent fashion and are most common when treatment is initiated. Sedation and other cognitive effects typically wane over time, and studies have demonstrated that most patients on chronic opioid therapy can safely drive cars.[41] If persistent sedation or cognitive impairment occurs, some patients are candidates for co-administration of a psychostimulant, such as dextroamphetamine, methylphenidate hydrochloride, or modafinil. The use of psychostimulants may be associated with side effects, however, and must be carefully monitored.

Adverse Reactions of Opioids

- Constipation
- Nausea
- Vomiting
- Sedation
- Mental clouding
- Impaired psychomotor function
- Respiratory depression
- Endocrine dysfunction (testosterone)

Opioids have the potential to interact with a variety of medications, primarily other CNS depressants with which additive effects occur. Increased sedation is a frequent interaction that has been reported with alcohol, benzodiazepines, butyrophenones, phenothiazines, sedative-hypnotics, tricyclic antidepressants, and anticonvulsants. Drug interactions are summarized in the Table: Important Opioid Drug Interactions.

Table: Important Opioid Drug Interactions

Opioid(s)	Interacting drug(s)	Effect
All	antihistamines, butyrophenones	Increased sedation
	tricyclic antidepressants	Increased sedation, potentiation of opioid-induced respiratory depression
Controlled-release opioids	metoclopramide	Earlier peak plasma concentration, increased sedation
Codeine	quinidine	Inhibition of conversion to morphine, decreased analgesia
Meperidine	monoamine oxidase inhibitors	Excitatory response (includes seizures, arrhythmia, hyperpyrexia)
Meperidine, morphine	cimetidine	Inhibition of opioid metabolism, increased opioid effects
Methadone	carbamazepine, erythromycin, phenytoin	Increased opioid metabolism, may induce withdrawal
Methadone, morphine	desipramine	Inhibition of desipramine metabolism, toxicity possible
Propoxyphene	carbamazepine	Increased carbamazepine levels, potential for toxicity
	doxepin	Increased doxepin levels, potential for toxicity
	metoprolol, propranolol	Increased plasma levels of these beta blockers

Source: Jackson KC, Lipman AG. Opioid Analgesics. In: Tallison CD, Satterwaite JR, Tollison JW, eds. *Practical Pain Management*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001; 216-231.

Monitoring Long Term Opioid Therapy

If long-term opioid therapy is administered, it is critically important to monitor outcomes systematically, and to change therapy if an indication to do so arises. These outcomes should be documented in the medical record repeatedly over time. There are four important types of outcomes:[41]

Analgesia. The effectiveness of the opioid for its primary indication, pain, should be assessed at regular intervals.

Adverse effects. Opioids carry a substantial side effect liability and therapy should not be continued if the burden posed by side effects is excessive.

Activities. Physical and psychosocial functioning must be assessed and documented during opioid therapy. During successful therapy, patients maintain their level of function or improve; therapy is unsuccessful if function declines.

Aberrant drug-related behavior. Problematic behavior occurs on a continuum and has a differential diagnosis. Relatively mild problems, such as the occasional use of an extra dose (particularly if not cautioned against this), must be contrasted with serious events, such as repeated requests for early refills, acquisition of prescription opioids from multiple sources, or the concurrent use of illicit drugs. Once aberrant behavior is identified, an assessment is needed to interpret it appropriately.[46]

Table: Examples of Adjuvant Analgesics Use

Indication	Examples
Multiple types of pain syndromes	Corticosteroids dexamethasone prednisone Tricyclic antidepressants* amitriptyline desipramine Selective serotonin and norepinephrine reuptake inhibitor (SNRIs) antidepressants* duloxetine minalcipran Alpha-2-adrenergic agonists clonidine* tizanidine* Topical therapies Local anesthetics
Neuropathic pain	Antiepileptic agents gabapentin pregabalin carbamazepine phenytoin valproic acid clonazepam lamotrigine topiramate tiagabine oxcarbazepine lacosamide NMDA receptor antagonists memantine ketamine dextromethorphan Oral sodium channel blockers mexiletine tocainide Miscellaneous baclofen calcitonin
Complex regional pain syndrome or suspected sympathetically maintained pain	Calcitonin Clonidine Prazosin
Bone pain from cancer	Bisphosphonates (*e.g.*,pamidronate) Calcitonin Radiopharmaceuticals

*Multipurpose drugs but used in neuropathic pain.
Adapted from Portenoy RK, Lesage P. Management of cancer pain. Lancet.1999; 353:1699.

Adjuvant Analgesics

Adjuvant analgesics (Table: Examples of Adjuvant Analgesic Use) are drugs that are used primarily for treating conditions other than pain, but may be analgesic in selected circumstances.[48] Adjuvant analgesics include agents useful in all types of pain (e.g. antidepressants), analgesics for neuropathic pain (e.g. antidepressants, and selected antiepileptic drugs (AEDs), and analgesics typically used for musculoskeletal pain (*e.g.* so-called muscle relaxants).

Antidepressants are multipurpose analgesics, appropriate for a trial in any persistent pain condition. The tricyclic antidepressants have been well studied and are most likely to be effective. The secondary amine tricyclic antidepressants, such as desipramine and nortriptyline, have a relatively favorable side effect profile and are generally preferred when an antidepressant of this type is tried for pain. A low starting dose (*e.g.*, 25 mg in adults and 10 mg in the elderly) should be gradually titrated upward. The usual effective dose range is 50-150 mg per day. Side effects include dry mouth, urinary retention, constipation, sedation, and orthostatic hypotension. The most serious side effects are cardiac rhythm disturbances, and patients should be carefully evaluated for cardiac abnormalities prior to initiating therapy.

The selective serotonin and norepinephrine reuptake inhibitors (SNRIs), specifically duloxetine and minalcipran, appear to be more effective analgesics than the selective serotonin reuptake inhibitors (SSRIs). Drugs that are predominantly noradrenergic, such as bupropion, also may be analgesic.

Antiepileptic agents are commonly used to treat neuropathic pain.[48] Gabapentin and pregabalin are currently the most commonly prescribed drugs for this indication. Pregabalin has more stable pharmacokinetics than gabapentin and should be more simple to use. Other antiepileptics, such as phenytoin, carbamazepine, clonazepam and valproic acid, and newer drugs, such as lamotrigine, topiramate, tiagabine, lacosamide, and oxcarbazepine, also are used as analgesics for refractory neuropathic pain. All of these drugs should be dosed and monitor in a manner similar to their use in seizure prevention.

An overview of adjuvant analgesics is provided in the Table: Adjuvant Analgesics for Persistent Nonmalignant Pain Conditions.

Table: Adjuvant Analgesics for Persistent Nonmalignant Pain Conditions

Drug Class	Starting Dose	Titration	Maximum Dose	Comments
Tricyclic anti-depressants				TCAs are multipurpose analgesics and may be considered for a trial in any type of persistent pain.[1-6] The analgesic effect of TCAs is separate from their antidepressant effects.[5] Depression also may be a target and doses sometimes require escalation to achieve this effect. The use of amitriptyline may be limited in many patients due to its side effects; desipramine and nortriptyline are preferred. A therapeutic response is usually seen within 3 to 10 days for neuropathic pain. TCA dosage should depend on the degree of pain relief balanced against the emergence of adverse effects. An adequate trial with a TCA needs to be given before determining treatment failure; some patients require higher dosages and several weeks of treatment before efficacy is evident. Failure of one TCA agent does not preclude a response to another, and two or more agents should be tried sequentially before selecting another class of adjuvant analgesic agents.
amitriptyline	10 to 25 mg qd	10 to 25 mg qd 3 to 5 days	100 to 150 mg/day	
desipramine	10 to 25 mg qd	10 to 25 mg qd	100 to 150 mg/day	
nortriptyline	10 to 25 mg qd	10 to 25 mg qd 3 to 5 days	100 to 150 mg/day	
SNRI				The newer norepinephrine/serotonin reuptake inhibitors (SNRIs) (e.g., duloxentine, venlafaxine) also may be considered multipurpose analgesics. Duloxetine has FDA-approved labeling for the management of pain caused by diabetic neuropathy. Side effects of SNRIs are usually less than those caused by the TCAs.
venlafaxine*	25 mg tid*	25 mg tid q >4 days*	225 mg/day*	
duloxetine	60 mg qd	---	120 mg/day*	
SSRIs				The selective serotonin reuptake inhibitors (SSRIs) have been used as adjunctive therapy for patients who are depressed. There is some evidence of analgesic efficacy (*e.g.*, paroxetine, citalopram) but it is limited. SSRIs have fewer side effects than TCAs and are generally considered safer. In patients with depression and persistent pain who cannot tolerate TCAs, a trial with an SSRI is reasonable. Experience is greatest with paroxetine and citalopram.
paroxetine*	20 mg/day*	10 mg/day q 7 days*	50 mg/day*	
citalopram*	20 mg/day* *antidepressant dose	20 mg/day q 7 days* *antidepressant dose	40 mg/day* *antidepressant dose	
Antiepileptic drugs				Antiepileptics are used in the management of neuropathic pain and are similar to TCAs in producing a graded analgesic effect.[7]
gabapentin	300 mg/day	300 mg bid,day 2 300 mg tid, day 3	1800 to 3600 mg/day or higher	Gabapentin and pregabalin have FDA -approved labeling for posthperpetic neuralgia. Most who respond to gabapentin do so at total daily doses of 900 to 1800 mg/day, but some patients require higher doses. Dose- related sedation is a limiting factor with gabapentin.
pregabalin (For PNH)	50 mg tid 75mg bid or 50 mg tid	100 tid after 1 week 100 tid after 1 week	300 mg/day 300 mg/day	Pregabaline has FDA-approved labeling for neuropathic pain associated with diabetic perpheral neuropathy.
carbamazepine	200 mg/day	200 mg/day q 12 h	1200 mg/day	Carbamazepine has FDA-approved labeling for trigeminal neuralgia. Oxcarbazine, topiramate, lamotrigine, tiagabine, and valproate have been reported to have effect against neuropathic pain based on case studies. These agents are typically used at their antiepileptic dosages.

GABA Agonist				The analgesic effect of baclofen in trigeminal neuralgia has led to wider use in neuropathic pain of other types.Although less effective than carbamazepine, the adverse-reaction profile forbaclofen is more favorable,making it an attractive initial drug to treat trigeminal neuralgia in select patients.The reported effective dosage range is 50 to 60 mg/d.[8]
baclofen	5 to 10 mg bid or tid	5 to 10 mg/day q 2 to 3 days prn	80 mg/day	
Oral sodium channel blocker				Mexiletine, an oral analog of intravenous lidocaine has been used to treat difficult to control neuropathic pain secondary to diabetic neuropathy, spinal cord injury,persistent pain syndromes secondary to peripheral nerve injury.[9-13]
mexiletine	150 to 200 mg bid	50 mg q 2 to 3 days prn	1200 mg/day	
Alpha-2-adrenergic				Sympatholytic agents are first-or second-line drugs for the intervals prn treatment of complex regional pain syndromes (CRPS). Most analgesic data support the effectiveness of intrathecal and epidural administration of clonidine.[14,15] The usual effective dosage is 0.3 mg/day. Transdermal clonidine may decrease swelling and pain in CRPS areas with hyperalgesia. Tizanidine is a muscle relaxant with centrally acting alpha-2 agonist activity. It can produce hypotension but this occurs less than with clonidine. Tizanidine may have some inherent analgesic activity.
agonist clonidine	0.1 mg bid	0.1 mg/day at weekly intervals prn	2.4 mg/day	
tizanidine	4 mg initially	2 mg q 6 to 8 hours	36 mg/day	
NMDA receptor antagonist				NMDA receptor antagonists can be useful in intractable neuropathic pain. The experience with dextromethorphan for persistent pain syndromes has been mixed.[16] One study has shown that dextromethorphan treatment improved pain assessment scores in patients with diabetic neuropathy but not PHN.[17] The optimal dose is unknown. The dose is likely to exceed the antitussive dose of 10 to 20 mg qid by a factor of 10. Doses in this range are inconsistently reported to be helpful and also are reported to produce significant adverse reactions. Ketamine, a dissociative anesthetic, has been used by pain specialists in some cases of intractable neuropathic pain. However, even with low (sub-anesthetic) doses, psychotomimetic side effects may limit its utility and safety, thus requiring careful patient selection.
ketamine	See comments	See comments	See comments	
dextro-methorphan	See comments	See comments	See comments	

Topical agents				Topical capsaicin has been used to treat a number of persistent pain conditions including diabetic neuropathy, PHN, osteoarthritis, rheumatoid arthritis, and postmastectomy pain.[18] One study concluded that topical capsaicin therapy for 22 weeks reduced pain in patients with diabetic neuropathy.[19] Patients should be instructed to use the lower strength concentration qid before attempting to use the higher strength concentration. Initial burning is common, but most patients become tolerant within a few days. Patients should be advised to wash hands thoroughly after using capsaicin and avoid contact with eyes and mucous membranes. Topical local anesthetics are also used commonly and lidocaine patch (5%) is available, with labeled indications for PHN,but used for other conditions as well. Up to 3 patches/day can be used.
capsaicin	0.025%to 0.075% qid	See comments	See comments	
lidocaine patch	lidocaine 5%	Up to 3 patches applied at once, for up to 12 hrs in 24 hr period	See comments	
Miscellaneous agent				Calcitonin, has been reported to reduce persistent pain associated with osteoporotic fractures, bone metastases, complex regional pain syndrome and phantom limb pain. Although the long-term efficacy has not been established, a trial of calcitonin may be considered in patients with refractory pain.
calcitonin, IM or SC	50 to 100 I.U./day	Maintenance dose 50 to 100 I.U.q 1 to 3 days	100 I.U./day	

1. McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain. 1996;68:217-227.
2. Lipman AG. Analgesic drugs for neuropathic and sympathetically maintained pain. Clin Geriatr Med. 1996;12:501-515.
3. Watson CP, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. Neurology. 1998;51:1166-1171.
4. Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. Neurology. 1988;38:1427-1432.
5. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. Neurology. 1995;45:S17-S25.
6. Calissi PT, Jaber LA. Peripheral diabetic neuropathy: current concepts in treatment. Ann Pharmacother. 1995;29:769-777.
7. Jacox AK, Carr DB, Chapman CR, et al. Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No 1. Rockville, MD: US Department of Health and Human Services; 1992. AHCPR publication 92-0032.
8. From GH. Clinical pharmacology of drugs used to treat head and face pain. Clin Neuropharmacol. 1990;8:143-151.
9. Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. Lancet. 1988;1:9-11.
10. Chiou-Tan FY, Tuel SM, Johnson JC, Priebe MM, Hirsh DD, Strayer JR. Effect of mexiletine on spinal cord injury dysesthetic pain. Am J Phys Med Rehabil. 1996;75:84-87.
11. Pfeifer MA, Ross DR, Schrage JP, et al. A highly successful and novel model for treatment of chronic painful diabetic peripheral neuropathy. Diabetes Care. 1993;16:1103-1115.
12. Strake H, Meyer UE, Schumacher HE, Federlin K. Mexiletine in the treatment of diabetic neuropathy. Diabetes Care. 1992;15:1550-1555.
13. Bach FW, Jensen TS, Kastrup J, Stigsby B, Dejgard A. The effect of intravenous lidocaine on nociceptive processing in diabetic neuropathy. Pain. 1990;40:29-34.
14. Maze M, Segal IS, Bloor BC. Clonidine and other alpha 2 adrenergic agonists: strategies for the rational use of these novel anesthetic agents. J Clin Anesth. 1988;1: 146-157.
15. Irving GA, Wallace MS. Pain Management for the Practicing Physician. New York: Churchill Livingstone; 1997.
16. McQuay HJ, Carroll D, Jadad A, et al. Dextromethorphan for the treatment of neuropathic pain: a double-blind randomized controlled crossover trial with integral n-of-1 design. Pain. 1994;59:127-133.
17. Nelson KA, Park K, Robinovitz E, Tsigos C, Max MB. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. Neurology. 1997;48:1212-1218.
18. Whittaker AL, Kennedy DT, Small RE. Adjuvant agents for managing chronic pain. APS Bulletin. 1999:9.
19. Tandan R, Lewis GA, Krusinsky BB, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy: controlled study with long-term follow-up. Diabetes Care. 1992;52:814.

References

1. Bonica JJ, Loeser JD. Medical Evaluation of the Patient with Pain. In: Bonica JJ, ed. *The Management of Pain.* 2nd ed. Philadelphia, PA: Lea & Febiger; 1990.
2. Portenoy RK, Kanner RM. Definition and assessment of pain. In: Portenoy RK, Kanner RM, eds. *Pain Management: Theory and Practice.* Philadelphia, PA: FA Davis; 1996:7.
3. Schaible HG. Peripheral and central mechanisms of pain generation. *Handb Exp Pharmacol.* 2007;(177):3-28.
4. Truini A, Cruccu G. Pathophysiological mechanisms of neuropathic pain. *Neurol Sci.* 2006 May;27 Suppl 2:S179-S182.
5. Parrott T. Pain Management in Primary-Care Medical Practice. In: Tollison CD, Satterthwaithe JR, Tollison JW, eds. *Practical Pain Management.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:729-759
6. Borenstein DG. Chronic low back pain. *Rheum Dis Clin North Am.* 1996;22: 439-456.
7. Cohen R, Chopra P, Upshur C. Primary care work-up of acute and chronic symptoms. *Geriatrics.* 2001;56:26-27.
8. Gamsa A. The role of psychological factors in chronic pain. I. A half century of study. *Pain.* 1994;57:5-15.
9. Pain Disorder. In: Frances A, Pincus HA, First MB, et al, eds. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 2000:498-503.
10. Au E, Loprinzi CL, Dhodapkar M, et al. Regular use of a verbal pain scale improves the understanding of oncology inpatient pain intensity. *J Clin Oncol.* 1994;12:2751-2755.
11. Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain.* 1993;55:195-203.
12. Banos JE, Bosch F, Canellas M, Bassols A, Ortega F, Bigorra J. Acceptability of visual analogue scales in the clinical setting: a comparison with verbal rating scales in postoperative pain. *Methods Find Exp Clin Pharmacol.* 1989;11:123-127.
13. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain.* 1983;17:197-210.
14. Wong DA, Mayer TG, Watters WC, et al. *North American Spine Society Phase III Clinical Guidelines for Multidisciplinary Spine Care Specialists.* LaGrange, IL: North American Spine Society; 2001.
15. van Tulder MW, Koes BW, Bouter LM. 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: 2128-2156
16. Kerns RD, Turk DC, Rudy TE. The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). *Pain.* 1985;23:345-356.
17. Ho M-J, LaFleur J. The treatment outcomes of pain survey (TOPS): a clinical monitoring and outcomes instrument for chronic pain practice and research. *J Pain Palliative Care Pharmacothera.* 19; 2004; 18(2): 49-59.
18. Sanders SH, Harden RN, Vicente PJ. Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic nonmalignant pain syndrome patients. *Pain Pract.* 2005 5:303-315.
19. Guzman J, Esmail R, Karjalainen K, et. al. Multidisciplinary bio-psychosocial rehabilitation for chronic low back pain. *Cochrane Database Syst Rev.* 2002;(1):CD000963.
20. Johnson RE, Jones GT, Wiles NJ,et. al. Active exercise, education, and cognitive behavioral therapy for persistent disabling low back pain: a randomized controlled trial. *Spine.* 2007;32:1578-1585.
21. Molton IR, Graham C, Stoelb BL, Jensen MP. Current psychological approaches to the management of chronic pain. *Curr Opin Anaesthesiol.* 2007;20(5):485-489.
22. McCracken LM,Turk DC.Behavioral and cognitive-behavioral treatment for chronic pain: outcome, predictors of outcome, and treatment process. *Spine.* 2002;27: 2564-2573.
23. Richardson J, Smith JE, McCall G, Pilkington K. Hypnosis for procedure-related pain and distress in pediatric cancer patients: a systematic review of effectiveness and methodology related to hypnosis interventions. *J Pain Symptom Manage.* 2006;31:70-84.
24. Khadilkar A, Milne S, Brosseau L, et. al. Transcutaneous electrical nerve stimulation for the treatment of chronic low back pain: a systematic review. *Spine.* 2005;30:2657-2666.
25. Licciardone JC, Brimhall AK, King LN. Osteopathic manipulative treatment for low back pain: a systematic review and meta-analysis of randomized controlled trials. *BMC Musculoskelet Disord.* 2005; 6:43.
26. Bronfort G, Haas M, Evans RL, Bouter LM. Efficacy of spinal manipulation and mobilization for low back pain and neck pain: a systematic review and best evidence synthesis. *Spine J.* 2004;4:335-356.
29. Ernst E. Chiropractic: a critical evaluation. *J Pain Symptom Manage.* 2008;35(5):544-562.
30. Manheimer E, White A, Berman B, Forys K, Ernst E. Meta-analysis: acupuncture for low back pain. *Ann Intern Med.* 2005 Apr 19;142(8):651-663.
31. Abdi S, Datta S, Trescot AM, et. al. Epidural steroids in the management of chronic spinal pain: a systematic review. *Pain Physician.* 2007;10:185-212.
32. Fitzgerald GA,. Prostaglandins, aspirin and other NSAIDS. In Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine,* 22nd ed. London: Elsevier Science; 2004:155-161.
33. Vane, J .R. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biology.* 1971 Jun 23; 231(25):232-235.
34. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. *Ann Intern Med.* 1991;115: 787-796.
35. Dubois RW, Melmed GY, Henning JM, Bernal M. Risk of upper gastrointestinal injury and events in patients treated with cyclooxygenase (COX)-1/COX-2 nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 selective NSAIDs, and gastroprotective cotherapy: An appraisal of the literature. *J Clin Rheumatol.* 2004;10:178-189.
35. Zapata-Colindres JC, Zepeda-Gomez S, Montano-Loza A, et. al. The association of Helicobacter pylori infection and nonsteroidal anti-inflammatory drugs in peptic ulcer disease. *Can J Gastroenterol.* 2006;20:277-280.
36. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA.* 2006;296:1633-1644.
37. Farkouh ME, Greenberg BP. An evidence-based review of the cardiovascular risks of the nonsteroidal anti-inflammatory drugs. *Am J Cardiol.* 2009;103(9):1227-1237.
38. Sowers JR, White WB, Pitt B, et al. The Effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and type 2 diabetes mellitus. *Arch Intern Med.* 2005;165(2):161-168.
39. Allen LV, Berardi RR, Desimone EM, et al., eds. *Handbook of Nonprescription Drugs.* 12th ed. Washington, DC: American Pharmaceutical Association; 2000.
40. Gladding PA, Webster MW, Farrell HB, et al. The antiplatelet effect of six nonsteroidal anti-inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. *Am J Cardiol.* 2008;101(7):1060-1063.
41. Haddox JD, Joranson D, Angarola RT, et al. The Use of Opioids for the Treatment of Chronic Pain: American Pain Society and the American Academy of Pain Medicine[consensus statement]. Available at: http://www.ampainsoc.org/advocacy/opioids.htm. Accessed January 17, 2003.
42. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* 2009;10(2):113-130.

43. American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain (6th ed). Glenview, IL: American Pain Society, 2008. Access at: http://www.painmed.org/pdf/controlled_substances_sample_agrmt.pdf
45. Fine PG, Portenoy RK, and the Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation. Establishing "best practices" for opioid rotation: conclusions of an expert panel. *J Pain Symptom Manage.* In press.
46. Andrews CM, Krantz MJ, Wedam EF, Marcuson MJ, Capacchione JF, Haigney MC. Methadone-induced mortality in the treatment of chronic pain: role of QT prolongation. *Cardiol J.* 2009;16(3):210-217.
47. Portenoy RK, Payne R, Passik S: Acute and chronic pain. In Lowinson JH, Ruiz P, Millman RB, eds. *Comprehensive Textbook of Substance Abuse.* Fourth Edition. Baltimore: Williams and Wilkins; 2005:863-903.
48. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med.* 2005;6:432-442.
49. Lussier D, Portenoy RK: Adjuvant analgesics. In Hanks G, Cherny NI, Christakis N, Fallon M, Kaasa S, Portenoy RK (eds): *Oxford Textbook of Palliative Medicine.* Fourth Ed. Oxford: Oxford University Press, in press.