

PAIN MANAGEMENT IN PATIENTS WITH SUBSTANCE-USE DISORDERS



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LEARNING OBJECTIVES

1. Construct a therapeutic plan to overcome barriers to effective pain management in a patient with addiction.
2. Distinguish high-risk patients from low-risk patients regarding use of opioids to manage pain.
3. Design a treatment plan for the management of acute pain in a patient with addiction.
4. Design a pharmacotherapy plan for a patient with coexisting addiction and chronic noncancer pain.
5. Design a pain management plan that encompasses recommended nonpharmacologic components for a patient with a history of substance abuse.

INTRODUCTION

Pain, which is one of the most common reasons patients seek medical care, is often undertreated. Addiction and pain are interrelated, with each condition influencing the treatment of the other. Patients with addiction have special clinical considerations and are at increased risk of receiving inadequate pain management. There are three broad categories of clinical considerations specific to this patient population. First, there are issues related to the addiction itself, such as abuse of opioids, altered pain perception, and adherence to pain drug therapy/monitoring. Next, there are issues

regarding drug interactions with illicit substances or prescribed pain medications. Finally, there are issues related to the comorbidities of the patient with addiction (e.g., psychiatric disorders or physical concerns related to the addiction) that should influence product selection.

Epidemiology

Pain is the second most common cause of workplace absenteeism. The prevalence of chronic pain may be much higher among patients with substance use disorders than among the general population. In the 2006 National Survey on Drug Use and Health, past-year alcohol addiction or abuse occurred in 10.3% of men and 5.1% of women. In the same survey, 12.3% of men and 6.3% of women were reported as having a substance-use disorder (abuse or addiction) during the past year. Men are more likely to use illicit drugs; they also have a higher incidence and prevalence of drug-use disorders, depending on the specific substance and age of use.

Nomenclature

Terminology in this area of medicine is often misused. The American Pain Society, the American Academy of Pain Medicine, and the American Society of Addiction Medicine have issued a joint consensus statement to define certain terms. *Addiction* is a primary, chronic,

BASELINE REVIEW RESOURCES

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Klipa D, Rousseau JC. Pain and its management. In: Koda-Kimble MA, Young LY, Alldredge BK, Corelli RL, Guglielmo BJ, Kradjan WA, et al, eds. *Applied Therapeutics: The Clinical Use of Drugs*. Philadelphia: Lippincott Williams & Wilkins, 2009:8-1–8-36.
- Pharmacists Recovery Network. Available at usaprn.org. Accessed December 7, 2010.
- Flannery B, Newlin D. Alcohol use disorders and their treatment. In: Smith HS, Passik SD, eds. *Pain and Chemical Dependency*. New York: Oxford University Press, 2008;131–6.

ABBREVIATIONS IN THIS CHAPTER

NSAID	Nonsteroidal anti-inflammatory drug
PCA	Patient-controlled analgesia
REMS	Risk Evaluation and Mitigation Strategy
SOAPP-R	Screener and Opioid Assessment for Patients with Pain – Revised
TENS	Transcutaneous electrical nerve stimulation

neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behavior that includes one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Although many expert groups and journals in the field commonly accept and use this term, a text revision of *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV-TR), uses a different term, *substance dependence*, to describe addiction. This term is confusing to patients and health care providers because of its similarity to the term *physical dependence*.

Physical dependence is an expected response to the chronic administration of many classes of drugs, including opioids, steroids, and β -blockers. Physical

dependence is a separate and distinct issue from the compulsive, consequential, drug-taking behaviors of addiction. Physical dependence is a state of adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreased blood concentration, and/or administration of an antagonist. Physical dependency is a neurologic condition. *Tolerance* is a state of adaptation in which exposure to a drug induces changes that result in a decrease of the drug's effects over time.

Addiction is a psychiatric condition associated with neurobiologic changes and behavioral manifestations. People with addiction often have both tolerance and physical dependency, but not all patients who are tolerant or physically dependent are addicted. Box 1-1 lists diagnostic criteria for substance dependence from the DSM-IV-TR.

Pseudoaddiction is a term used to describe aberrant drug-seeking behaviors in patients with undertreated pain. In pseudoaddiction, the behaviors resolve with adequate pain relief. For clarity, the term *addiction* is used in this chapter.

PATHOPHYSIOLOGY

Pain

Nociception is the process of communication between a site of tissue damage and the central nervous system. The four steps in the process are as follows:

Box 1-1. DSM-IV-TR Diagnostic Criteria for Substance Dependence: Addiction

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period:

1. Tolerance as defined by either of the following:
 - a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect
 - b. A markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal as manifested by either of the following:
 - a. The characteristic withdrawal syndrome for the substance (refer to criteria A and B of the criteria sets for withdrawal from the specific substances)
 - b. The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
3. Substance often taken in larger amounts or for a longer period than was intended
4. A persistent desire or unsuccessful efforts to cut back on or control substance use
5. Much time spent on activities necessary to obtain the substance (e.g., visiting many doctors, driving long distances), use the substance (e.g., chain-smoking), or recover from the effects of the substance
6. Important social, occupational, or recreational activities given up or reduced because of substance use
7. Substance use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Information from American Psychiatric Association Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR)*, 4th ed. Washington, DC: APA Press, 2000.

transduction (nociceptors convert stimulus energy into electrical nerve impulses), transmission (nerve impulses travel from periphery to spinal cord and brain), perception (brain and spinal cord appreciate nerve impulses), and modulation (descending input from brain influences spinal cord nociception). Neuropathic pain is caused by the abnormal processing of nerve impulses in the periphery or central nervous system.

Addiction

Addiction is a pathophysiologic brain adaptation to the repeated use of psychoactive drugs over time. The common element in the action of these drugs is their impact on brain reward pathways. The reward pathways mediate response to natural rewards necessary to sustain life such as food and sex. Drugs of abuse activate these reward pathways at an intensity above that of natural rewards. With time, this repeated intense stimulation causes adaptations that lead to two major consequences. First, the diminished response to natural rewards leads to a need to use the drug to feel “normal.” Second, the emotional memories associated with drug use remain during months to years of abstinence. Drug-associated environmental cues or stressful events can trigger intensive craving and relapse, in part by activating the brain’s reward pathways through the presence of these memories.

Interface Between Addiction and Pain

Physiologic states common in patients with addiction can affect nociceptive input, processing, and/or modulation. Chronic use of addictive drugs may affect the processing of pain stimuli through sympathetic stimulation, hypothalamic-pituitary-adrenal axis dysregulation, and opioid tolerance. Addictive disease appears to augment the experience of pain, and evidence suggests that people with addictions have decreased pain tolerance. The presence of both conditions can result in a reorganization of baseline perceptual pathways in the brain that results in increased pain perception.

Personality traits of patients with addiction, such as an external locus of control and a tendency to perceive circumstances as worse than they are or to expect the worst to happen, have been associated with poorer outcomes in patients with pain. Intoxication and withdrawal both activate the sympathetic nervous system, which augments the patient’s pain perception. This activation of the sympathetic nervous system also results in increased muscle tension, irritability, and anxiety, further contributing to discomfort.

Withdrawal is associated with a negative affective state caused by dopamine depletion in the brain that exacerbates discomfort in patients with addiction. In addition, these patients often experience interpersonal conflicts and loss of social support that are detrimental to adequate pain management.

SCREENING AND BARRIERS

Identification of High-Risk Patients

The risk of developing addiction in the course of treating acute pain is very small in the general population. Some studies of long-term opioid therapy in patients with chronic pain suggest the risk of addiction or select aberrant behaviors related to opioid misuse is minimal (about 3%); however, no patient may be free from the risk of addiction. Additional precautions are required when patients identified as being at high risk of developing substance abuse disorders are prescribed opioids. A universal precautions approach to managing pain is recommended to minimize addiction risks.

It is difficult to ascertain which patients are at highest risk of developing addiction to opioids. Several studies of high-risk predictors have been reported in the literature with conflicting results. The strongest high-risk predictor consistently reported is a personal history of alcohol and illicit drug abuse. Other predictors, studied less often but established as positive predictors, are a family history of drug and illicit drug abuse, a history of childhood sexual abuse, a history of convictions for driving under the influence or drug-related offenses, lost or stolen prescriptions, and the use of supplemental sources to obtain opioids. It is also important to recognize symptoms during the course of therapy that may indicate emerging addiction.

Several clinical tools have been developed to assist in identifying high risk in patients being considered for or currently receiving long-term opioid therapy. The Current Opioid Misuse Measure is a tool that assesses a patient’s relative frequency of a thought or behavior in the past 30 days. The Screener and Opioid Assessment for Patients with Pain – Revised (SOAPP-R) is a tool designed to predict future misuse based on past behavior or thoughts; this tool is only appropriate for patients under consideration for long-term opioid therapy. Clinicians can use the SOAPP-R and the Current Opioid Misuse Measure in tandem to identify high-risk patients who require more intensive monitoring at different stages of chronic long-term opioid therapy.

Potentially aberrant symptoms can occur at times in a patient on chronic opioid therapy. However, persistent or frequent symptoms are of concern. Alert signs include persistent euphoria or increasing sedation, decreasing functional level despite adequate pain relief, or increased psychiatric symptoms such as anxiety, depression, or insomnia. Attempts to obtain early refills, use opioids from illicit sources, or go “doctor shopping” for additional prescriptions indicate either addiction or pseudoaddiction. Preoccupation with opioid use is a core feature of addiction. This preoccupation may result in patients who are nonadherent to lifestyle and other nonopioid pain relief modalities and who believe that nothing but opioids will relieve their pain.

Barriers to Care

Issues that decrease either patient or provider access to therapy may compromise the quality of care in patients with both pain and addiction. The Controlled Substances Act gives the Drug Enforcement Administration authority to regulate controlled prescription drugs. In addition, new Risk Evaluation and Mitigation Strategy (REMS) programs are in development for opioids. The goal of opioid REMS programs is to promote the appropriate use of opioids; these programs are likely to include mandatory physician education and increased documentation. Many pain management health care providers are concerned that the restrictions associated with REMS programs for opioids will decrease access to care for patients with pain.

State regulations allow for opioid prescription monitoring programs. Many of these programs are also accompanied by restrictions on prescribing. Prescribing patterns can be reviewed by regulatory and other authorities. These programs have led to debate regarding what is and is not legitimate medical practice. Fear of sanctions by state medical boards can be a barrier to physicians prescribing opioids when needed. The Federation of State Medical Boards developed model guidelines that describe professional standards for appropriate opioid prescribing. These standards have been adopted by many state medical boards.

Another barrier to care is physician attitudes of distrust toward patients with pain, particularly the patient with a history of substance use. This barrier leads to less-than-optimal pain treatment. If the patient is undertreated and consequently exhibits signs of pseudoaddiction, assessment and management of pain become even more difficult. It is critical for all parties to openly acknowledge the history of substance abuse. The first step in forming a plan to address the patient's pain is to obtain accurate knowledge of the patient's current and past substance use.

Other methods for overcoming the patient-physician lack of trust barrier include being attentive to withdrawal concerns, relapse triggers, and comorbid conditions, and increasing patient assessment and monitoring. It is helpful to establish a therapeutic relationship not only with the patient but also with his/her family. Family members can potentially help the patient avoid failure by monitoring adherence to the drug therapy and nonpharmacologic components of the treatment plan, holding the patient accountable for his/her actions, and being a source of information for the practitioner.

TREATMENT GOALS

Therapy goals for pain management in the general patient population are as follows: minimize physiologic adverse effects of unrelieved pain, avoid adverse

effects of therapy, maximize nonpharmacologic treatment approaches, improve quality of life, and educate about self-care of pain. Patients with opioid addictions have an additional set of goals because of the complexity of their clinical circumstance (Box 1-2).

It is important for any patient with chronic pain and the clinician to understand that the complete absence of pain may not be a realistic goal, but a decrease in pain to facilitate increased functioning is likely to be attainable. Patients should set personal goals for therapy based on their activities of daily living (e.g., participating in family events, attending church, maintaining a job). The patient whose only goal is to be pain free may consider treatment a failure if that state is not achieved and therefore be more likely to self-medicate. Self-medication can lead to a full-blown relapse of addiction and a consequent lack of adherence to the global treatment plan.

Therapeutic success can be compromised by many errors on the part of patients and practitioners. Setting unrealistic goals and giving insufficient time for an intervention to work are common errors. A practitioner can err by imposing overly tight restrictions on opioids, resulting in inadequate pain relief that in turn leads to drug-seeking behaviors by the patient, which leads to further restrictions in pain drugs. This vicious cycle can prevent therapeutic success.

PAIN MANAGEMENT

Opioids

Opioids are the drugs of choice in managing severe pain, including acute postsurgical or trauma-induced pain and cancer pain. Their role in the management of chronic noncancer pain is not clearly defined. Physicians have expressed several concerns regarding opioid prescribing, including prescription drug abuse, addiction, adverse effects, tolerance, and drug interactions. Conflicting literature is available on the long-term benefits of opioids for treatment of chronic noncancer pain. Findings from a recent controlled study of primary care patients over

Box 1-2. Pain Management Goals of Therapy for Patients with Opioid Addiction

Prevent withdrawal

Treat symptoms

Provide effective analgesia

Prevent relapse to addiction

Effective treatment of opioid addiction (maintenance opioid therapy)

Treatment of psychiatric disorders such as anxiety

Information from Mehta V, Langford RM. Acute pain management for opioid dependent patients. *Anaesthesia* 2006;61:269–276.

6 years suggest that low-dose morphine (20–40 mg of morphine or equivalent daily) improve quality of life in patients with pain compared with patients not receiving opioid therapy. In contrast, a large epidemiologic study from outside the United States reported decreased quality of life in patients with pain who were on long-term opioid therapy.

A systematic review was conducted in the development of Canadian guidelines on the use of opioids for chronic noncancer pain. Strong and weak opioids were more effective for pain than placebo regardless of the type of pain (neuropathic or nociceptive), and they worked better for treating pain than for improving function. Opioids have small to moderate benefits for nociceptive pain of musculoskeletal origin (e.g., osteoarthritis, low back pain, neck pain), and patients usually respond to moderate doses. Opioids have small to moderate benefits in neuropathic pain as well, but patients with this type of pain often require high-dose opioids and concomitant therapy with tricyclic antidepressants or anticonvulsants. Because of a lack of evidence, opioids were not recommended for migraine or tension headaches or for functional gastrointestinal problems such as irritable bowel disease. Tramadol has evidence of a small benefit in patients with fibromyalgia. More evidence is needed to facilitate our understanding of which types of patients with chronic pain would achieve the best outcomes with opioid therapy.

One clear benefit of opioid use in short-term pain management is the rapid onset of relief. One of the disadvantages of use for long-term pain management is the inevitable development of tolerance and the consequent negative perception by the patient and providers that the patient's drug use is escalating. The expense to our health care system associated with treatment and complications of addiction is well documented. Expenditures necessary for adequate pain management in these patients help prevent the cost to the system associated with relapse.

Opioid Use Considerations in Patients with Substance-Use Disorders

Use of opioids for acute pain is unlikely to have a long-term effect on the course of a patient's addiction unless the patient is in remission at the time of opioid use; opioids may trigger relapse in these patients. Relapse has also been attributed to inadequate pain relief, so opioid use in these patients may be necessary along with appropriate monitoring.

Reward is attenuated to some degree in most patients in the presence of pain regardless of the patient's prior or current use or abuse of opioids. Hyperalgesia has been documented in opioid-dependent populations and is manifested by increased pain caused (instead of relieved) by high-dose opioid therapy. Withdrawal should be prevented in patients who are not in remission

at the time of a short-term pain episode. Alcohol withdrawal may produce signs that are interpreted as increased pain levels (e.g., tachycardia), whereas opioid withdrawal produces additional pain and anxiety.

There are special considerations regarding the adverse effects of opioid use in opioid-dependent patients. Respiratory depression is less common in these patients than in the general population because tolerance of this effect occurs sooner than does tolerance of the therapeutic effects. Respiratory depression can be seen when doses of long-acting agents such as methadone and levorphanol are titrated or when opioid agents are rotated. Respiratory support should be used instead of naloxone to manage respiratory depression, if possible, because of the risk of precipitating withdrawal with naloxone use.

Risks associated with opioid use should be discussed with the patient before initiating therapy. The patient is likely to focus on the risk of withdrawal and/or relapse much more than other adverse effects that may be of greater concern in the general patient population.

Opioid Selection Considerations

Both global concepts (e.g., pharmacokinetics) and individual patient factors are important when selecting opioids for managing pain in patients with addiction. Recent research provides evidence that a patient's therapeutic and adverse response to a specific opioid is influenced by pharmacogenomics. Patient-specific differences in μ and other receptor subtypes can influence a patient's therapeutic and reward response to a certain opioid.

Meperidine and propoxyphene are recognized as poor choices in the general population, and the same is true in patients with addictions. Mixed agonist-antagonist agents (pentazocine, nalbuphine, butorphanol) may reverse analgesia and precipitate withdrawal in opioid-dependent patients. These patients are most often tolerant to the μ receptor effects, so the ceiling effect of the mixed agonist-antagonist agents precludes their use.

Buprenorphine and tramadol are partial μ agonists that have clinical utility in patients with addiction. Tramadol is not free of addiction potential, and it is a drug of choice for many patients in substance abuse treatment centers. It effectively has an analgesic ceiling because of its potential for causing seizures at doses above 400 mg/day. Tramadol, like other opioids, has been associated with serotonergic syndrome. Buprenorphine can be used as an analgesic when dosed at 6-hour to 8-hour intervals, but it may exhibit a ceiling effect that limits its use in patients with the most severe pain. Practitioners presenting at conferences specific to the issue of substance dependence in health care professionals report using buprenorphine to treat pain in patients with addiction. Pure opioid agonists remain the best choice of therapy for many patients with

pain despite the presence of addiction. There are some important considerations when selecting a pure agonist agent. Chronic pain should not be managed solely with short-acting opioids in patients with substance-use disorders; a wearing-off effect may occur near the end of the dosing interval, resulting in withdrawal symptoms and increased pain perception. Onset of action should also be considered. Rapid onset of action is a critical property identified to contribute to potential for abuse. If the controlled-release properties of an opioid product are altered, the patient receives a rapid peak concentration. Controlled-release forms of opioids, when taken as intended, provide less fluctuation in serum concentrations. Scheduled dosing obviates the need for the patient to make a decision to take the opioid in response to perceived pain.

An important concept in pain management in the general population is the provision of both a long-acting agent on a scheduled basis and a short-acting agent on an as-needed basis for breakthrough pain. This approach can be problematic in patients with addiction because administration of the drug is associated with pain relief and reinforces the behavior of taking additional doses of opioids. Two alternative approaches in the patient with addiction can be used to avoid this reinforcement. The first is to schedule doses of a short-acting agent at times of the day when the patient is most likely to experience breakthrough pain. The second is to premedicate with the short-acting product 30 minutes before an activity that is known to increase pain. One strategy for minimizing problems associated with the use of short-acting agents is to have a family member or friend dispense the drug per dose or per day. Scheduled dosing decreases the perception of the person administering the drug that the patient is drug seeking. Use of short-acting agents may be minimized in some patients through the use of nondrug interventions and activity pacing. Short-acting agents for unpredictable breakthrough pain may be necessary in some patients.

Important acute pain opioid selection considerations include pharmacokinetics and administration route. Intravenous access may be an issue in patients with a history of injectable drug abuse. Peak concentrations of the opioid relative to the patient's tolerance level provide an important determinant of the level of reward caused by a given opioid dosage form. Intravenous administration provides a rapid onset of effects and high serum drug concentrations when given as intermittent boluses, enhancing the rewarding effects of the drug. Intravenous administration of opioids is less rewarding when administered as a continuous infusion.

Opioid withdrawal can be avoided by administering a baseline dose of opioid that corresponds to the patient's usual opioid use in addition to opioids required to address the pain. Another option in a hospitalized patient is the administration of methadone to prevent

withdrawal in addition to opioids for pain management. Although patient-controlled analgesia (PCA) devices involve self-administration and as-needed dosing by the patient, they are useful for pain relief in this population. A PCA pump provides small incremental doses that help maintain a more stable serum concentration than intravenous bolus administration. If a patient has a high tolerance level, a continuous infusion of opioids or a long-acting oral opioid may be required in addition to the PCA. If the patient is in remission and therefore has no potential for withdrawal, use of intraspinal anesthesia may be the best choice. If the patient is not in remission, intraspinal opioids may be an option as long as a baseline systemic dose of an opioid is maintained to avoid withdrawal.

An important opioid selection consideration in patients with chronic pain is the drug's half-life. Levorphanol and methadone have long half-lives and *N*-methyl-D-aspartic acid receptor antagonist activity that may help lessen the development of tolerance. Methadone has a wide-ranging half-life and must be titrated carefully to avoid excessive accumulation and oversedation. Methadone has many drug interactions that can result in QT prolongation.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are primarily useful for somatic pain of mild to moderate intensity and are usually not effective for neuropathic pain. These agents can be useful adjuncts to low-potency opioids in the management of severe pain. Nonsteroidal anti-inflammatory drugs have dual mechanisms for pain relief and act both in the periphery and in the central nervous system with effects independent of their anti-inflammatory properties. The adverse effects of NSAIDs are of concern in patients with addictions who have comorbid complications secondary to abuse.

Antiplatelet and gastrointestinal effects of NSAIDs are significant dangers to patients with hepatic disease. Patients with cirrhosis are prone to excessive bleeding and have a high incidence of gastric varices and/or ulceration. Choline magnesium trisalicylate has less antiplatelet effect than other NSAIDs. Proton pump inhibitors should be used with NSAIDs to protect patients from gastrointestinal adverse effects. This therapy is preferable to using a cyclooxygenase-2 selective NSAID because of potential cardiovascular risks associated with these agents. Lithium serum concentrations in patients with concomitant bipolar disease and addiction will be affected by an NSAID-induced decrease in renal clearance.

Antidepressants

Tricyclic antidepressants are useful in the management of most neuropathic pain. Evidence suggests that tricyclics modulate pain pathways and enhance the effect of opioids at their receptors. Patients with

addictions are often impulsive and gravitate toward immediate gratification; they should be counseled that it usually takes several weeks before the full effect of the drug therapy is realized. They should also be aware that tolerance of many of the initial unpleasant anticholinergic adverse effects of the drugs may develop.

The mixed neurotransmitter reuptake agents venlafaxine and duloxetine are effective for neuropathic pain and are associated with fewer falls, fewer anticholinergic effects, and no cardiac conduction disturbances. Recent trials with duloxetine showed its effectiveness in diabetic peripheral neuropathy at dosages of 60 mg once or twice daily as well as in fibromyalgia with or without concomitant depression. In the presence of concurrent depression and neuropathic or nonspecific pain, duloxetine and venlafaxine are first-line choices on the basis of recent trials. Duloxetine should be avoided in patients with hepatic disease. Clinicians should be aware that duloxetine has been associated with serotonergic syndrome. Venlafaxine should be used with caution in patients with hypertension.

Anticonvulsants

Many antiepileptic drugs are effective in treating neuropathic pain, even though their exact mechanisms of action are not fully understood. Anticonvulsants have a slow onset of pain relief, and the patient may not fully appreciate the full effects for several weeks after therapy initiation. The efficacy of anticonvulsant agents may be very different from their effectiveness because of pronounced adverse effects.

Phenytoin can be administered as a 1-g loading dose for acute pain, and the average maintenance dosage for acute or chronic pain is 300 mg/day. The efficacy of carbamazepine for chronic pain is superior to phenytoin, and dosing can be initiated at 100 mg/day and increased in increments of 100 mg every 3–7 days to minimize the dizziness often associated with both phenytoin and carbamazepine therapy. Both anticonvulsants share the adverse effect of somnolence, which may lessen over time as the patient acclimates to anticonvulsant therapy. Failure to tolerate the sedative effects of anticonvulsants in the early stages of therapy is a common reason for treatment failure. Patients who are not in remission from addiction are often nonadherent to drug therapy or the necessary laboratory monitoring associated with these narrow therapeutic index drugs. Rates of human immunodeficiency virus (HIV) are higher among patients with substance-use disorders than among the general population, and the potential adverse impact of carbamazepine and phenytoin on blood counts make them unfavorable choices for these patients. Patients on methadone maintenance therapy are very sensitive to small changes in the serum concentration of methadone, so they should avoid the use of phenytoin because of its drug interaction profile.

Gabapentin is often effective for the management of neuropathic pain and can be dosed starting at 100 mg at bedtime, with 100-mg to 300-mg increases in dose every 3–5 days with a maximal dosage of 3600 mg/day. Patients with addiction commonly suffer from insomnia that causes a decreased level of alertness and ability to concentrate during the day. The daytime somnolent effects of gabapentin may be more pronounced in these patients during the first 2 weeks of therapy until tolerance develops. Recent clinical trials have shown that gabapentin in dosages of 900–1200 mg/day is effective when used preoperatively to reduce the opioid requirement postoperatively and reduce opioid adverse effects.

A recent pregabalin trial provided evidence for use of this agent in the management of diabetic neuropathy. When used to manage various types of neuropathic pain, pregabalin should be dosed initially at 50 mg three times/day and increased to 100 mg three times/day for 7 days. Dosages up to 600 mg/day may be required, with an average dosage of 450 mg/day in fibromyalgia. Dizziness, weight gain, somnolence, edema, and thrombocytopenia are the adverse effects of note for pregabalin.

Clonazepam has also shown efficacy as a treatment for neuropathic pain. It is not a first-line choice because of concerns about benzodiazepine use leading to craving and relapse. It is also associated with dysphoria and is a poor choice for the patient with concurrent depression.

Anesthetics

Lidocaine infusion inhibits spontaneous C fiber activity associated with inflammation. Lidocaine can be infused at a dose of 5 mg/kg over 30 minutes, resulting in pain relief that may last for several days. Repeat infusions may not achieve an equal response. Mexiletine is effective at high doses for treatment of neuropathic pain. Prescribers should initiate therapy with 150 mg/day and increase the dosage by 150-mg increments every 3–5 days up to a dosage of 300 mg three times/day. Adverse effects include sedation, dizziness, nausea, and tremor. Hematologic reactions are rare, making this a useful option in patients with blood dyscrasias.

Mexiletine has an onset of pain relief much more rapid than that of anticonvulsant and antidepressant agents. Although clinical trials have shown mexiletine to be effective, adverse effects limited patient acceptance. In a study using survival analysis to determine factors that predicted continued therapy with mexiletine, the median time to discontinuation of mexiletine was only 53 days. Characteristics predictive of continuing mexiletine therapy long term were male sex, younger age, and a positive response to lidocaine infusion. These findings illuminate the difference between the clinical efficacy, as reflected by conventional end points such as changes in pain score, and the clinical utility of a drug with limited patient acceptance. Mexiletine is an acceptable agent to use in an effort to explore nonopioid

options in patients with addiction who have not adequately responded to first-line neuropathic pain agents or who have blood dyscrasias.

Topical Agents

Topical agents can be useful in patients with substance abuse disorders as an adjunct to other therapeutic modalities that provide incomplete relief of predominantly peripheral pain. Use of topical agents may help avoid the need to initiate opioid therapy. Topical amitriptyline and ketamine were compared in a randomized, double-blind, placebo-controlled trial for efficacy in neuropathic pain. The primary outcome measure was change in daily average pain intensity using an 11-point pain rating scale. Secondary outcomes measures included the McGill Pain Questionnaire, patient satisfaction, and measures of allodynia and hyperalgesia. Each therapy and the combination of both agents achieved a good response.

Lidocaine 5% patches were as effective as naproxen for carpal tunnel pain and were preferred by patients. Lidocaine patches can be useful for a variety of neuropathic pain types and have few adverse effects (primarily local irritation). Patches should be worn for 12 hours/day. Capsaicin and eutectic mixture of local anesthetics prilocaine and lidocaine are effective in some patients with neuropathic pain, especially those with pain in small areas. The use of both agents together (administer eutectic mixture of local anesthetics prilocaine and lidocaine first) may be an alternative in patients who find the burning sensation associated with capsaicin intolerable. Topical agents are listed as potentially effective alternatives in current diabetic neuropathy guidelines but are not among the recommended first- or second-tier agents.

Muscle Relaxants

Baclofen, tizanidine, and benzodiazepines are spasmolytic agents used for muscle spasm because of neural injury. Cyclobenzaprine, carisoprodol, methocarbamol, and chlorzoxazone have muscle relaxant effects through central nervous system depression, not a true antispasmodic action. The literature lacks sufficient evidence to support using these agents in pain management, and most should be avoided in patients with addictions because of their potential for abuse.

Interventional Injections/Blockade

Mechanical and procedural options offer alternatives to opioid use pain management in patients with substance-use disorders. These options may avoid adverse effects or suboptimal efficacy associated with daily oral therapy. Trigger point injections have been used for myofascial pain. Botulinum toxin A and bupivacaine were compared in a double-blind randomized crossover trial of patients with myofascial pain syndrome who

were participating in a home exercise program. Efficacy and patient satisfaction were similar in both groups.

Lumbar facet injections achieve short- and long-term pain relief in select patients with neck or back pain. The long-term benefit of corticosteroid epidural injections is moderate at best according to a position statement by the American Academy of Neurology.

Procedures that provide sympathetic blockade (e.g., targeted bupivacaine injections) can provide relief for pain involving the sympathetic nervous system and the viscera. Abnormal sympathetic activity may be a source of complex regional pain syndrome. Bupivacaine injection is superior to local temperature modulation in patients with complex regional pain syndrome. Bupivacaine blocks achieve complete or partial pain relief in 76% of patients, with a shorter duration of relief associated with a longer duration of complex pain syndrome. The evidence does not yet support the use of sympathetic blockade as the standard of care. On the basis of recent trials, spinal cord stimulation may be an alternative in patients with addictions and unrelieved back pain or angina pectoris pain. Spinal cord stimulation requires surgical intervention to implant a device to deliver electrical stimulation; thus, it should not be considered a first-line therapy.

Botulinum toxin provides pain relief in patients with pain induced by dystonia or muscle spasm. Adverse effects include local reactions or unacceptable weakness of muscle groups that can result in gait disturbances. Injections, which usually do not last longer than 3 months, must be repeated, and the long-term effects of repeat injections are unknown.

Lifestyle and Physical Therapies

In a recent trial of patients with low back pain, heat application was most effective when combined with exercise. Cold application may reduce local inflammation and muscle spasm and may be more effective than heat in acute pain. Transcutaneous electrical nerve stimulation (TENS) is a nondrug option for patients with addiction and joint, neck, or other acute pain, but it is less effective for back pain. In a placebo-controlled trial of 200 patients with chronic back pain, those randomized to TENS showed improvements in pain and neck strength. The TENS therapy should be used in conjunction with physical therapy.

Exercise is beneficial in many types of chronic pain to decrease pain and increase functionality. Patients should be encouraged to set functional goals because exercise may initially result in increased pain.

Acupuncture can be applied by needling, heat, pressure, or electrical stimulation. Acupuncture modulates nerve fiber firing and stimulates release of endorphins. Recent studies support the use of acupuncture in osteoarthritis and fibromyalgia. There is more evidence to support the use of acupuncture for somatic pain than

for neuropathic pain. Acupuncture is a safe and viable treatment option for patients with addiction.

MANAGEMENT OF ACUTE PAIN IN THE PATIENT WITH OPIOID ADDICTION

Few randomized, controlled trials of acute pain in patients with opioid addiction have been performed, so the evidence comes primarily from case reports, retrospective studies, and expert opinion. Clinically, it can be helpful to classify patients with opioid addiction experiencing pain as follows: (1) patients with an active addiction who are currently using heroin and/or prescription opioids (includes patients who are prescribed opioids for chronic pain and have an active addiction); (2) patients who are currently in remission from addiction and who are receiving opioid substitution therapy with methadone or buprenorphine; and (3) patients who are currently in remission but not receiving opioid substitution therapy. Another group requiring special consideration when needing short-term treatment with opioids is patients with chronic pain who require maintenance opioid therapy and who are therefore physically dependent as expected, but who do not have an addiction. Because this chapter focuses on patients with substance-use disorders, this last group is not considered here.

Understanding the concepts of pain intolerance, opioid tolerance, and withdrawal prevention is essential to deliver effective analgesia in patients with substance-use disorders who are currently opioid-dependent (groups 1 and 2 above). Opioid-dependent patients have a measurable degree of pain intolerance and increased sensitivity during cold pressor and thermal testing. These changes may lead to increased opioid requirements for effective pain relief. In addition, the issue of opioid tolerance must be considered. Patients on long-term opioid therapy commonly require higher doses of opioids to achieve analgesia. Cross-tolerance to opioids varies widely among patients. This variability necessitates extreme caution when substituting one opioid for another to gain better pain control or compensate for baseline opioid use during a short-term pain episode.

Prevention of withdrawal is best accomplished if the patient receives an amount equivalent to his/her daily opioid dose plus additional opioids to provide effective analgesia. Clinicians must gain the patient's trust to get an accurate history of the dose and type of opioids he/she habitually consumes.

Patients on Opioid Replacement Therapy

Patients on methadone maintenance therapy should receive their usual daily dose of methadone plus a different opioid agent for management of the acute pain. It is best to avoid conversion of methadone to an equianalgesic dose of a different opioid because variations in

cross tolerance can result in ineffective analgesia and/or withdrawal effects. Methadone is not an ideal agent for acute pain management because of its wide-ranging half-life and potential for causing delayed respiratory depression during dosage titration. Maintenance of the usual methadone dose in combination with a different agent to manage acute pain offers the advantage of keeping the two issues (prevention of withdrawal and pain management) separate and distinct.

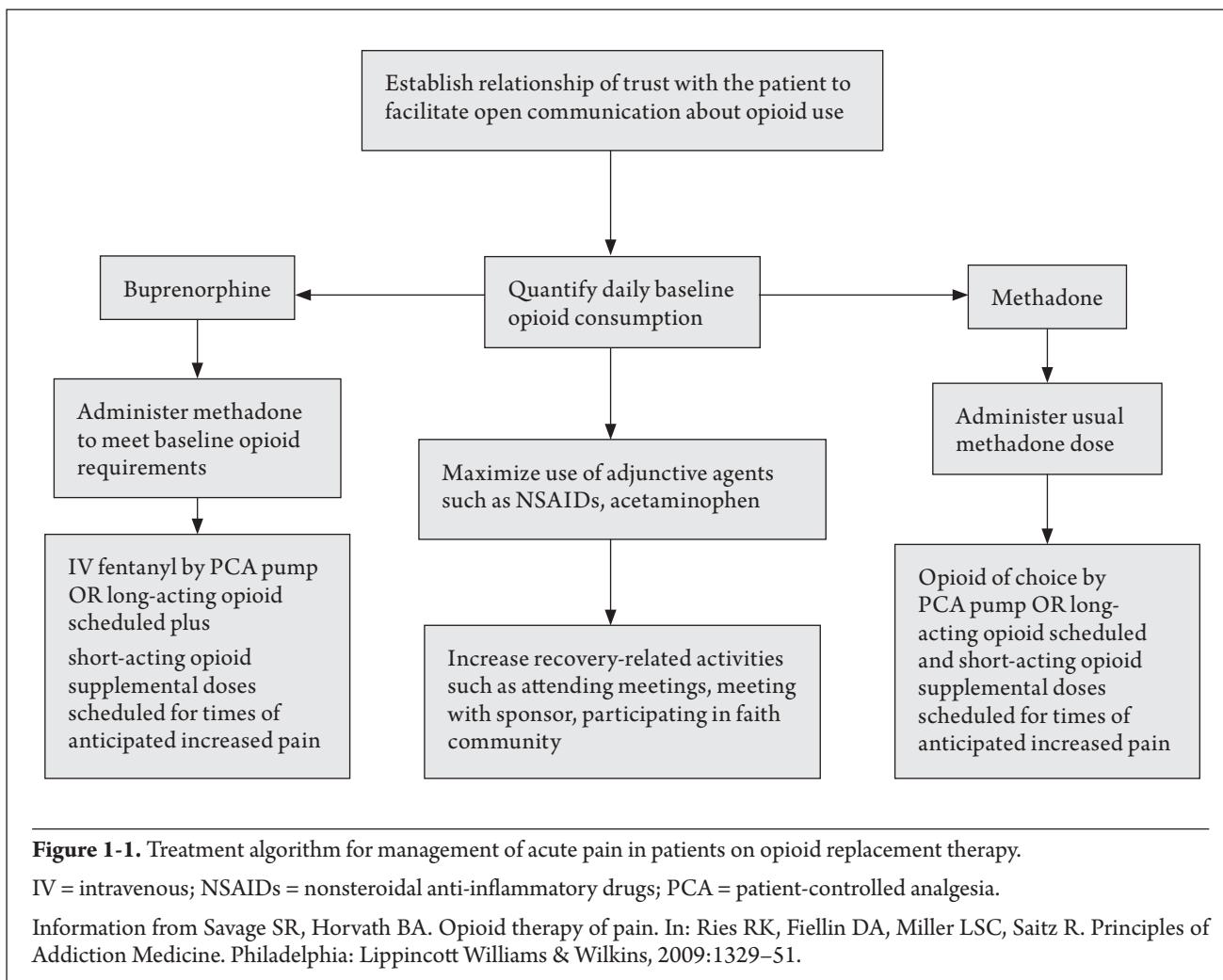
If the exact usual dose of methadone cannot be confirmed with the patient's methadone maintenance clinic, it is advisable to divide the total daily dose reported by the patient into three or four increments so he/she can be monitored for adverse effects after each dose. Intravenous methadone dosing should be done with caution because of the poor predictability of the oral bioavailability of the drug. The usual oral daily dose should be cut in half when administered intravenously. Subcutaneous doses of methadone should be one-half to two-thirds the daily oral dose of methadone.

Recent literature suggests that patients on methadone maintenance therapy require substantially more opiate analgesia after cesarean delivery than control patients. In one retrospective trial, patients on methadone maintenance therapy required 70% more opiates to manage pain than controls on the basis of oxycodone equivalents administered during a 72-hour period postpartum.

A different strategy is preferred if the patient is maintained on buprenorphine therapy. Buprenorphine binds strongly to μ and k receptors and may prevent additional analgesics from being effective. If the acute pain episode is anticipated (e.g., surgical pain), buprenorphine should be discontinued for several days before the episode and supplemented with methadone to prevent withdrawal. If the pain is unanticipated (e.g., from trauma) and it is not possible to discontinue the buprenorphine, use of an intravenous form of an opioid that binds strongly to μ receptors, such as fentanyl, is preferred (see Figure 1-1) Sufentanil is an analog of fentanyl that is 10–15 times more potent than fentanyl. Higher doses of opioids are often necessary to overcome the buprenorphine occupation of receptors, so very close monitoring of the patient is required. If a patient is on very low-dose buprenorphine, it may be possible to increase the daily buprenorphine dose and split administration into four doses to achieve an analgesic effect. When buprenorphine/naloxone is discontinued to manage anticipated pain with a full opioid agonist, the clinician should carefully change the patient back to buprenorphine/naloxone to prevent precipitating opioid withdrawal.

Peri- and Postoperative Considerations

Opioid-dependent patients scheduled for surgery should be instructed to take their usual dose of oral opioid (including methadone) on the morning of surgery



with a sip of water. If the patient did not take an opioid at baseline, a roughly equivalent loading dose of morphine or hydromorphone can be administered preoperatively as an oral elixir or intravenously, either at the induction of anesthesia or during the operation. If the patient is wearing a fentanyl patch, it should be kept on during surgery. If it is removed sooner than 12 hours before surgery completion, an intravenous fentanyl infusion is indicated. A new patch should be applied intraoperatively, but bridging with an agent having a more rapid onset of action will be necessary because of the slow onset of transdermal fentanyl. The fentanyl infusion rate can be tapered during the patch's onset of action.

Although it is acceptable to use systemic opioids for analgesia in opioid-dependent patients, local anesthetics offer an alternative. Doses of local anesthetic agents should be reduced in patients with hepatic dysfunction or hypoalbuminemia. Multimodal analgesia is acceptable and may be required to achieve pain control.

Postoperative analgesia by epidural routes alone is usually not advisable in patients dependent on opioids

because withdrawal symptoms will develop owing to the lack of systemic opioids. One case report documented use of epidural sufentanil that successfully managed pain and prevented withdrawal symptoms in a methadone-dependent patient with cancer.

If the patient receives long-term opioid therapy in implantable devices (intrathecal or epidural), maintain their use during the perioperative period except for intrathecal devices containing baclofen. Baclofen's central effects and peripheral skeletal muscle relaxant action may enhance neuromuscular blockade and contribute to hypotension or unacceptable levels of sedation.

Nonopioid Alternatives for Perioperative Analgesia

Limited data exist on the use of dexmedetomidine as an analgesic alternative or adjunct to opioids. If more evidence reveals that dexmedetomidine is effective in these roles, use of this agent may be particularly advantageous in the perioperative pain management of patients with alcohol addiction. Dexmedetomidine is an α_2 -agonist approved for use in intensive care unit

sedation. It is 10 times more potent than clonidine and has a half-life of about 2.3 hours. Dexmedetomidine is effective in the management of postoperative pain and alcohol withdrawal syndrome. There are case reports of patients with alcohol addiction in whom dexmedetomidine was used to maintain analgesia after induction with an opioid agent. No opioids were administered intraoperatively or postoperatively, and the patients remained calm and comfortable.

Use of dexmedetomidine permits limiting the use of opioids and benzodiazepines, both of which have been reported in case reports to stimulate alcohol craving in recovering alcoholics. The analgesic effects of dexmedetomidine have been reported as a secondary end point in trials and, in one small trial, were evaluated as the primary end point. This clinical trial compared dexmedetomidine with morphine in 34 surgical patients. Infusion of dexmedetomidine during the intraoperative period reduced the need for morphine by 66% and was associated with a slower heart rate during recovery. This beneficial effect did not extend to the 24 hours after the patient's transfer to the floor, however, so the overall opioid-sparing effect of this agent is questionable.

PATIENT EDUCATION AND SUPPORT SYSTEMS

A primary goal of pain management in patients with addiction is to control pain while avoiding withdrawal and relapse. Additional measures are required in this patient population to support this goal. Selection of treatment modality may be influenced by the risks associated with opioid therapy. More invasive and/or expensive options can be used earlier in therapy to minimize opioid use. Earlier use of long-acting opioids is preferable, even though they may be more expensive, because the use of short-acting opioids has a greater propensity to stimulate craving and relapse. The patient's goal of avoiding relapse can also be supported by limiting the quantities of opioids dispensed to the patient at a single time. Increasing recovery-related activities can be a considerable source of support for many patients. This might take the form of meeting more often with a 12-step program sponsor or group, becoming more active in a faith community, or increasing daily readings and journaling.

The frequency of monitoring should be increased compared with pain patients who do not suffer from addiction. Increased monitoring of tests such as urine drug screens to detect illicit substances can be helpful in providing accountability to support the patient's goal of maintaining recovery. Some evidence suggests that patient populations who undergo routine urine drug screens as part of an overall adherence monitoring program have a reduced prevalence of illicit drug use during long-term opioid therapy. Pill counts are another

tool supportive of accountability and therefore recovery. If there is concern that the patient may be diverting the prescribed agent to purchase an alternative drug of choice, an opioid challenge test can be performed in a closely supervised setting. The patient should have intravenous access established, and a supply of opioid antagonist should be available. The patient should then receive his/her usual dose and be observed carefully throughout the onset and peak effect.

A recent study at a Veterans Affairs medical center showed that with appropriate support, many patients with continuing substance use or aberrant behaviors can successfully manage their pain. In this study, patients attended consultations with clinical pharmacists, signed "second-chance" agreements, and were subject to many of the other support measures previously mentioned. Forty-five percent of the patients in the study were able to remain in the pain management program with their behavior controlled to an acceptable level.

Patient contracts are advisable for any patient with a history of substance abuse who is initiating opioid therapy. The contract should clearly specify expectations of the patient and the provider, including reasons for which opioid therapy will be discontinued. Contracts commonly stipulate a greater intensity and frequency of monitoring than is standard for patients at lower risk of aberrant drug behaviors. Family members should become educated about both addiction and pain and can be enlisted to provide monitoring, support, and dispensing of drugs.

For patients with addiction experiencing pain who are pharmacists, pharmacist recovery networks can provide monitoring and accountability, and most such networks have formal arrangements with the local state board of pharmacy. Other health care professionals (e.g., physicians and nurses) also have respective recovery groups with connections to the local licensing board that can provide support and accountability. It is important for the pharmacist with a substance abuse disorder to be known to the local pharmacist recovery network and/or board of pharmacy, both for the benefit of the pharmacist with the addiction and for public safety. If the pharmacist is known only to an employee assistance program, a change in job will result in not receiving the support he/she requires, and the public will not be protected. If a pharmacist with an addiction and concomitant pain shows aberrant drug behaviors, the most appropriate place to report these behaviors is to the state board of pharmacy through a pharmacist recovery network, if one is available, or directly to the board of pharmacy, if no pharmacist recovery network exists.

QUALITY IMPROVEMENT

It is important for pain patients to understand that a pain-free state is an unrealistic therapeutic end point.

Realistic outcomes for patients with chronic pain include substantial pain reduction, increase in functional ability, increased quality of life, and decreased psychological complications of chronic pain. Patients should be assessed for signs of functional impairment such as inability to participate in household chores or to leave the house to participate in activities and increased time spent reclining or remaining in nightclothes. Use of the Sheehan Disability Scale can help quantify functional impairment and document response to treatment.

CONCLUSION

Pain management in patients with substance use disorders is a complex, challenging, and common clinical scenario. Clinicians must be attentive to all the considerations common to any patient with pain, as well as to the special considerations of this patient population. Patients and prescribers often have attitudes and fears that are barriers to quality care and increase the chance of suboptimal therapy. Open communication and increased monitoring are important components of caring for patients with substance use disorders.

ANNOTATED BIBLIOGRAPHY

1. Meyer M, Wagner K, Benvenuto A, Plante D, Howard D. Intrapartum and postpartum analgesia for women maintained on methadone during pregnancy. *Obstet Gynecol* 2007;110:261–6.

Opioid-dependent patients on methadone maintenance therapy require higher doses of analgesia after cesarean section than control patients. This study evaluated whether analgesic requirements can be expected to be higher in patients on methadone maintenance therapy during the intrapartum and postpartum periods. Sixty-eight patients treated with methadone for opiate dependency during pregnancy were matched retrospectively to control women. Thirty-five of the patients maintained on methadone had vaginal deliveries, and 33 underwent a cesarean section. The primary outcome was cumulative opiate use expressed as oxycodone equivalents, and secondary outcomes were self-assessed pain scores and intrapartum analgesia. This study found a statistically significant difference in pain scores between the patients maintained on methadone maintenance therapy and the patients in the control group during both vaginal and cesarean delivery. This difference did not result in greater opioid use intrapartum in the methadone group, but it did result in a 70% increase in opioid use ($80.1 \text{ mg} \pm 48.4$ vs. $47.2 \text{ mg} \pm 19.1$; $p < 0.001$) in the postpartum period among women on methadone maintenance therapy who delivered by cesarean section. These findings suggest that greater than normal doses of opioids are necessary for effective management of cesarean section-induced acute pain in patients on methadone maintenance therapy.

2. Pain Management Without Psychological Dependence: A Guide for Healthcare Providers. Substance Abuse in Brief Fact Sheet. 2006. Volume 4. Issue 1. Substance Abuse and Mental Health Services Administration. U.S. Department of Health and Human Services. Available at http://kap.samhsa.gov/products/brochures/text/saib_0401.htm. Accessed December 7, 2010.

This fact sheet provides a brief overview of several critical concepts regarding pain management and the interface with substance dependence. It includes many references and a resource list that guides the reader to further information on a variety of related issues such as regulatory and substance abuse treatment information. Nonopioid therapy options and important opioid therapy considerations are discussed, as are barriers to prescribing opioids for pain and strategies to reduce the risk of psychological dependence on opioids. Signs of inappropriate opioid use by patients are listed, along with suggestions for actions to take if a pattern of these signs develops. The fact sheet also provides practical information on counseling patients suspected of having substance-use problems.

3. Barry D, Beitel M, Joshi D, Schottenfeld R. Pain and substance-related pain-reduction behaviors among opioid dependent individuals seeking methadone maintenance treatment. *Am J Addict* 2009;18:117–21.

These research findings could have implications for planning pain management services in conjunction with methadone maintenance programs. Some 293 subjects applying for enrollment in methadone maintenance programs were asked to complete an anonymous survey as part of the screening process at the initial appointment. Subjects were told the survey answers would not affect their methadone treatment at the clinic. The brief survey assessed the prevalence of pain types (recent vs. lifetime history of chronic pain), characteristics of pain (intensity, frequency), substance-related pain reduction behaviors, and demographics. On the basis of answers to the pain-related items, subjects were classified into two pain groups: (1) no recent pain (in the past 7 days) or (2) recent pain (only in the past 7 days). The recent pain group was subdivided into the two groups: (1) moderate pain intensity with lifetime history of chronic pain; or (2) moderate pain intensity without lifetime history of chronic pain. Of the study subjects, 88% reported recent pain. This illustrates the need for practitioners to understand appropriate management of short-term pain in patients on opioid replacement therapy. The results are consistent with studies examining pain in patients currently enrolled in methadone maintenance therapy. Eighty-three percent of those who reported recent pain characterized their pain as moderate to severe based on a 5-point scale. Sixty-six percent of subjects who reported recent pain of at least moderate intensity reported a lifetime history of chronic pain. Subjects who reported recent pain of moderate intensity reported no marked difference in substance-related pain reduction behavior (i.e., using more than the prescribed amount of opioids) among the group with lifetime pain and the group without lifetime pain.

- Many subjects reported greater use of benzodiazepines than prescribed or use of benzodiazepines that were not prescribed at all. Clinicians working with pain patients on methadone maintenance therapy should be aware that benzodiazepines may be used for self-management of pain. Patients should receive education about the overdose and sedation dangers of concomitant unmonitored medical use of benzodiazepines and methadone.
4. Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res* 2006;6:46.
- This study of 196 patients with chronic, noncancer pain treated with opioids helps delineate patients for whom the risk-benefit ratio of opioid use is less favorable based on the risk of opioid misuse. Opioid misuse was defined as abnormal drug screens (absence of prescribed opioids, presence of controlled substances not prescribed by research prescribers, or presence of stimulants such as cocaine or amphetamines), evidence of "doctor shopping," opioid diversion, or prescription forgery. Patients were recruited from within an academic internal medicine practice. Patients signed a medication agreement on enrollment that facilitated data collection through review of clinical history, medications, outside medical records, and communication with pharmacies and providers in addition to urine toxicology screens. The mean patient age was 55 years, and most subjects were white men. Predictors of misuse identified on multivariate analysis included younger age, past cocaine abuse, driving under the influence or other drug-related conviction, and past alcohol abuse. There was no evidence of a correlation between pain scores and misuse. Race, income, education, depression score, disability score, and literacy were also unassociated with misuse. One limitation of this study was the failure to assess a correlation between family history and risk of misuse. This study suggests that patients with a history of alcohol or cocaine abuse or related convictions should be carefully monitored for signs of misuse when opioids are prescribed.
5. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med* 2005;6:107–12.
- This article describes the components of universal precautions as the term applies to pain management. The authors provide a triage scheme for classifying patients into risk categories and recommendations for management and referral. A summary of the 10 steps of universal precautions in pain medicine are as follows. (1) Make a diagnosis (address comorbid conditions). (2) Perform a psychological assessment including risk of addictive disorders (urine drug screening should be considered). (3) Gain informed consent. (4) Prepare a treatment agreement (patient contract is important to set boundaries and to make early identification and intervention around aberrant behavior possible). (5) Perform a pre- and postintervention assessment of pain level and function. (6) Perform an appropriate trial of opioid therapy plus or minus adjunctive drugs. (7) Reassess pain score and level of function. (8) Regularly assess the four A's of pain medicine (analgesia, activity, adverse effects, and aberrant behavior), and document a fifth A (affect). (9) Periodically review pain diagnosis and comorbid conditions, including addictive disorders. (10) Provide documentation. Patients can be stratified into three risk categories to determine which patients' pain can be managed in a primary care setting. Group I (primary care patients) have no substance-use disorder or history of it and a noncontributory family history. Group II (primary care patients with specialist support) may have a history of a treated substance-use disorder or a significant family history of problematic drug use. They may also have a past or current psychiatric disorder. Group III (specialty pain management) patients are the most complex because of an active substance-use disorder or a major untreated psychopathology.
6. Apolone G, Corli O, Negri E, Mangano S, Montanari M, Geco MT, et al. Effects of transdermal buprenorphine on reported outcomes in cancer patients: results from the Cancer Pain Outcome Research study (CPOR) study group. *Clin J Pain* 2009;25:671–82.
- This study evaluated the efficacy of transdermal buprenorphine in patients with cancer. This was a multicenter, open-label, prospective, nonrandomized study with 1801 subjects. The primary outcome of the study was pain intensity as measured by the 11-point rating scale of the Brief Pain Inventory. Thirty-four percent of subjects on transdermal buprenorphine reported at least a 2-point improvement in "worst pain" scores, 20% reported improvement in pain relief, and 40% reported improved satisfaction with pain management. This study is limited by its observational design, but it does suggest that further, better-designed comparative studies of transdermal buprenorphine are warranted. It also suggests that this delivery method is likely to be received well by patients. Transdermal buprenorphine could become an important therapeutic tool for pain management in patients with any type of addiction whose pain does not exceed buprenorphine's ability to treat. A transdermal buprenorphine formulation was approved in the United States in 2010 for use in chronic pain at a dose not to exceed 20 mcg/hour. Buprenorphine sublingual formulation is typically dosed at 8–16 mg/day as an opioid replacement therapy.
7. Chou R, Fanciullo G, Fine P, Adler J, Ballantyne J, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 2009;10:113–30.
- These guidelines were issued jointly by the American Pain Society and the American Academy of Pain Medicine based on a systematic evidence review of data from adult patients on long-term opioid therapy. The guidelines were developed in recognition of the legitimate medical need for opioids in some patients with chronic noncancer pain but also in recognition of the growing incidence of prescription opioid misuse and mortality associated with opioid use. These

guidelines recommend that patients be assessed before a trial of long-term opioid therapy for the potential risk-benefit ratio based on screening tools such as the SOAPP-R and indication for pain management. Clinicians are advised to obtain informed consent from the patient before initiating long-term opioid therapy. The guidelines advocate the use of a patient contract. Specific monitoring recommendations are offered on the basis of the patient's risk stratification. The recommendations range from monitoring once every 3–6 months for low-risk patients to monitoring weekly for patients at very high risk. Monitoring tools such as random urine drug screens, prescription monitoring program data, pill counts, caregiver interviews, and instruments designed to detect aberrant drug-related behavior are advocated. The use of chronic opioid therapy in patients with a history of substance abuse is considered appropriate in some circumstances, with additional monitoring and consultative services from an addiction medicine specialist if possible. Guidelines are offered for opioid rotation and discontinuation. Evidence was not presented regarding specific disease states for which chronic opioid therapy would be appropriate.

8. Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) guidelines. *Pain Physician* 2008;11:S5–S62.

These guidelines were issued to address inconsistencies in philosophy among different groups regarding opioid use in chronic noncancer pain, to improve pain management, and to decrease the incidence of abuse and drug diversion. An extensive review of the literature resulted in recommendations graded using the U.S. Preventive Services Task Force criteria. The guidelines include a broad range of information including terminology, pharmacology, documentation recommendations, and adherence monitoring. The best evidence for effectiveness of long-term opioids in reducing pain and improving functional status for 6 months or longer is for transdermal fentanyl and sustained-release morphine. Transdermal fentanyl patches are not appropriate as initial therapy in opioid-naïve individuals. In patients with substance-use disorders, sustained-release morphine is a better choice than fentanyl because of concerns about tampering and the potency of fentanyl. The weakest evidence for long-term use of opioids is for methadone and hydrocodone. A sample patient contract is included in the guidelines, as is information about urine drug tests.

9. Edlund MJ, Martin BC, Devries A, Fan MY, Brennan B, Sullivan MD. Trends in use of opioids for chronic non-cancer pain among individuals with mental health and substance use disorders: the TROUP study. *Clin J Pain* 2010;26:1–8.

This study compared the use of prescription opioids for chronic noncancer pain in two patient populations, those with mental health and substance abuse disorders

and those without. Patients with mental health or substance abuse disorders have often been excluded from opioid trials, so little evidence exists about the relative risk versus benefit of using opioids in this patient population. Data were collected from two sources: Arkansas Medicaid enrollees and a national commercially insured group of patients. Patients were included on the basis of ICD (International Classification of Diseases) codes for back pain, neck pain, joint pain, headache, or HIV/AIDS (acquired immunodeficiency syndrome); age (at least 18 years old); and enrollment in the insurance program (enrolled for at least 9 months). Exclusion criteria included patients with a cancer diagnosis, nursing home residents, and hospice patients. Chronic opioid therapy was defined as receiving greater than a 90-day supply of opioids during the calendar year. Rates of opioid use, doses, and types of opioids prescribed were evaluated. In both the Medicaid and commercially insured populations, there was a statistically significant difference in the chronic use of opioids for noncancer pain between patients with and without mental health and substance abuse disorders. Patients with mental health disorders showed greater chronicity of use and a greater increase in use during a 5-year period of the study. Limitations of this study include the reliance on administrative diagnosis with no clinical assessment of patients, the exclusion of opioids bought over the Internet or purchased illegally, and indistinguishability of methadone used for maintenance therapy from methadone used for pain management. This study illustrates that a patient population most at risk of addiction is also receiving the greatest amount of opioids.

10. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med* 2006;144:127–34.

This article provides a concise review of common misconceptions of health care providers that result in undertreatment of acute pain in patients receiving opioid-replacement therapy. The article discusses the pharmacokinetic and pharmacodynamic factors involved in the lack of analgesia patients receive from opioid replacement therapy alone, including the concepts of tolerance and opioid-induced hyperalgesia. The authors compare the risk of relapse from use of opioids for analgesia in patients on opioid-replacement therapy with the risk of relapse associated with unrelieved pain. The authors address concerns regarding the additive effects of opioid analgesics and opioid-replacement therapy. The article includes a discussion of the desire to avoid manipulation by drug-seeking patients. General recommendations for the provision of pain management in patients on opioid replacement therapy are provided, as well as information specific to each of the two most commonly used opioid-replacement agents (methadone and buprenorphine).

SELF-ASSESSMENT QUESTIONS

1. A 32-year-old woman is admitted to the hospital for surgical repair of a broken femur from a motor vehicle crash. In the operating room she received 2 mg of morphine by mouth. Six hours later she rates her pain as 9/10 and complains of nausea and inability to take drugs intravenously. Her medical history is significant for heroin use for 10 years before attaining remission from substance dependence. Her only home medication is methadone 100 mg by mouth daily as part of a methadone maintenance program. **Which one of the following is the most appropriate choice to treat this patient's pain?**
 - A. Methadone 90 mg subcutaneously daily plus ketorolac 30 mg intramuscularly now.
 - B. Methadone 120 mg subcutaneously daily plus morphine 5 mg intravenously every 4 hours.
 - C. Methadone 50 mg intravenously daily plus morphine patient-controlled analgesia (PCA).
 - D. Methadone 90 mg intravenously daily plus morphine 2.5 mg intravenously every 4 hours.
2. A 52-year-old man presents to the pain clinic with a history of degenerative disc disease and a current pain score of 8/10 secondary to a recent occupational back injury. He has been receiving morphine 15 mg orally twice daily for 5 years. He is married, and his mother had an alcohol addiction. He reports occasional use of marijuana but no other illicit drugs. **Which one of the following is most predictive of this patient's risk of displaying aberrant drug behaviors in response to opioid pain management?**
 - A. Duration of morphine use.
 - B. Pain intensity of 8/10.
 - C. Current use of marijuana.
 - D. Family history of substance abuse.
3. A 26-year-old woman who has been on methadone maintenance therapy during her pregnancy presents to the hospital for a scheduled cesarean section. She does not plan to breastfeed her baby. Her home medications include methadone 100 mg orally daily. **Which one of the following would best address this patient's anticipated postpartum pain?**
 - A. Methadone 100 mg orally on the day of surgery plus oxycodone/acetaminophen 10/650 mg every 6 hours postoperatively.
 - B. Buprenorphine 8 mg on the day of surgery plus oxycodone/acetaminophen 7.5/650-mg dose every 4 hours postoperatively.
4. Methadone 100 mg intravenously on the day of surgery plus oxycodone/acetaminophen 10/650-mg dose every 4 hours postoperatively.
5. Fentanyl patch 100-mcg dose placed the day of surgery.
6. A 32-year-old woman suffers chronic pain from injuries sustained in an industrial accident 6 months ago. She has a 15-year history of marijuana use and reports current use on weekends. Ibuprofen 800 mg orally every 6 hours failed to control her pain. Her primary care physician is concerned about prescribing long-term opioids for her because of her history of illicit substance use. **Which one of the following is most likely to minimize the addiction risk associated with chronic narcotic therapy in this patient?**
 - A. Make a patient contract between the physician and the patient.
 - B. Establish a relationship with her family members.
 - C. Limit narcotics prescribed to tramadol and propoxyphene.
 - D. Use low-dose, low-potency narcotics.
7. A 32-year-old woman has been maintained on daily buprenorphine and naloxone as opioid replacement therapy for 2 years. She has an appointment for sinus surgery next week. She has been in remission with no history of psychoactive drug use during the past 2 years. **Which one of the following is the most appropriate strategy to manage this patient's anticipated surgical pain?**
 - A. Buprenorphine and naloxone orally on the day of surgery plus morphine intravenously postoperatively.
 - B. Methadone orally daily for 7 days before and including the day of surgery, plus sustained-release morphine postoperatively.
 - C. Buprenorphine and naloxone orally on the day of surgery plus methadone orally postoperatively.
 - D. Methadone orally on the day of surgery plus buprenorphine orally postoperatively.
8. A 52-year-old man who suffered from active alcohol dependence for 15 years entered remission 6 months ago. His medical history includes diabetes, refractory hypertension, heart failure, gastric varices, ascites, and cirrhosis. He presents with pain in both feet that he describes as "like stepping on pins

and needles" and that occurs on a daily basis. He has unsuccessfully tried to relieve the pain at home with acetaminophen and warm water soaks. **Which one of the following is the best initial therapy for this patient's pain?**

- A. Duloxetine.
 - B. Pregabalin.
 - C. Venlafaxine.
 - D. Gabapentin.
7. A 42-year-old woman is hospitalized secondary to injuries sustained in a motor vehicle crash 6 hours ago. She has taken methadone 80 mg/day orally as opioid replacement therapy for 1 year after a 10-year history of heroin use. Her medical history is otherwise nonsignificant, and she takes no other home medications. **Which one of the following is the most appropriate strategy for managing this patient's acute pain?**
- A. Methadone 80 mg orally on the day of surgery plus methadone orally every 8 hours.
 - B. Methadone 40 mg intravenously on the day of surgery plus morphine 10 mg orally every 4 hours postoperatively.
 - C. Morphine sustained release in an equianalgesic dose to methadone 80 mg orally on the day of surgery plus immediate-release morphine orally postoperatively.
 - D. Methadone 80 mg orally on the day of surgery plus morphine intravenously by PCA pump postoperatively.
8. A 27-year-old woman sustained several broken bones in a motor vehicle crash that required surgical intervention in February. She was prescribed hydrocodone 5 mg plus acetaminophen 500 mg three times/day as needed on hospital discharge. She presented to her usual pharmacy three times in March requesting early refills, and her profile revealed she had narcotics from different prescribers filled in March, also. When questioned, the patient said that she had not been truthful with the prescribers about the amount of narcotics she already had and that she had taken narcotics purchased on the street. She stated her bone pain keeps her awake at night, making it hard to concentrate during the day with only the original narcotic she was prescribed. She presents to the pharmacy again in May to pick up a narcotic refill, and a review of her profile reveals that she has not filled a narcotic prescription in several weeks, even though she submitted a prescription in April that was never picked up. A quick check with other pharmacies in the small town confirms that she has not filled narcotic prescriptions elsewhere. The patient reports that her pain is much better now, and she uses the hydrocodone prescribed for her only occasionally. **Which one of the following is the best assessment of this patient's clinical circumstance?**
- A. She is an addict who has reverted to the use of street drugs primarily.
 - B. Her drug-seeking behaviors of early refills, use of illicit drugs, and obtaining opioid prescriptions from several providers prove she is an addict.
 - C. Her behavior is typical of pseudoaddiction because the undesirable behaviors decreased as her pain decreased.
 - D. She was tolerant of opioids after hospitalization but has returned to her baseline response to opioids and, consequently, requires less now to control her pain.
9. A 53-year-old man with a 15-year history of opioid addiction was admitted to the intensive care unit 2 weeks ago for extensive injuries received in a motor vehicle crash. He reported daily use of opioids before this hospitalization, and required high-dose opioids during his complicated hospital stay. He is being discharged today to an addiction treatment program. He is expected to suffer chronic pain as a result of his injuries. **Which one of the following is the best recommendation to manage this patient's pain after discharge from the acute care hospital?**
- A. Morphine 30 mg sustained release twice daily plus morphine immediate release 30 minutes before activities associated with increased pain.
 - B. Methadone 80 mg orally at bedtime plus morphine immediate release every 3 hours as needed.
 - C. Fentanyl 75-mcg patch every 72 hours plus morphine immediate release every 4 hours as needed.
 - D. Methadone 70 mg orally daily plus hydrocodone 7.5 mg and acetaminophen every 6 hours.
10. A 33-year-old woman has chronic leg pain from a crush injury sustained in a motor vehicle accident years ago. She was maintained on methadone 30 mg three times/day at a pain clinic for 5 years. At that time, her average pain intensity was 2/10. She had no history of seeking early refills or additional prescriptions from different physicians. She moved to a new city and established care with a family medicine physician, who is concerned about prescribing "too much narcotics." This physician

changed her regimen to 7.5 mg of hydrocodone and 500 mg of acetaminophen twice daily. She sought early refills on her hydrocodone prescription in 3 of the last 4 months, claiming that she had lost the bottle or someone stole her it from her. Telephone calls to area pharmacies reveal that she has filled many hydrocodone prescriptions from several local physicians. When confronted with this information, she becomes tearful and states that she finds it hard to sleep at night or go to work when her pain is so intense. She rates her pain level while receiving the new analgesic regimen as 9/10. **In addition to discontinuing her current medications, which one of the following is the best choice for treating this patient's pain?**

- A. Tramadol.
 - B. Oxycodone/acetaminophen.
 - C. Methadone.
 - D. Nonsteroidal anti-inflammatory drug.
11. A 55-year-old man has just relocated with his family to a new state. He presents to a family medicine clinic to establish care with a new primary care provider. He is seeking management of gastroesophageal reflux disease, hypertension, and chronic back pain. He has a 30-year history of alcohol and opioid abuse. He is concerned about the physician's willingness to address all of his problems or accept him as a patient if the physician is aware of his substance abuse history. The physician is concerned about not contributing to drug-seeking behaviors and the liability involved with prescribing narcotics. **Which one of the following is the best initial step in constructing a therapeutic plan to overcome barriers to this patient's care?**
- A. Engage in frank, nonjudgmental, two-way dialogue regarding substance use.
 - B. Document current substance use.
 - C. Assess risk factors predictive of aberrant drug behaviors.
 - D. Establish a relationship with the patient's family.
12. A 42-year-old man suffers from alcoholism and chronic low back pain. His alcohol addiction has been in remission for 7 years. His job as a postal carrier in a dense urban environment requires him to walk 5–6 miles each day while carrying heavy loads. He has been maintained on morphine sustained release 30 mg two times/day for several years; this resulted in a pain level of 3/10 and ability to continue performing his job. His pain has been increasing during the past several months. He currently assesses the level at 6/10, which makes it difficult for him to perform his job. He is reluctant

to change opioids or increase the dose, saying he is afraid of the potential to "switch" his drug of choice from alcohol to opioids if the dose is increased or has a lesser analgesic effect with a different agent. **Which one of the following is best to add to this patient's current regimen?**

- A. Transcutaneous electrical stimulation.
 - B. Trigger point injections.
 - C. Botulinum toxin injections.
 - D. Spinal cord stimulation.
13. A 51-year-old woman has alcohol dependence, cirrhosis, gastric varices, chronic kidney disease, and chronic neck pain. She self-assesses her pain as 6/10. She has tried unsuccessfully to treat her neck pain with over-the-counter naproxen sodium, heating pads, and glucosamine/chondroitin. **Which one of the following is the best recommendation to manage this patient's chronic pain?**
- A. Ibuprofen 800 mg orally three times/day.
 - B. Tramadol 100 mg orally every 6 hours/day.
 - C. Cyclobenzaprine 10 mg orally every 8 hours daily.
 - D. Morphine sustained release 15 mg orally every 12 hours.
14. A 42-year-old woman presents to a family medicine clinic complaining of tingling and burning in her lower extremities. Her medical history includes diabetes, hypertension, opioid addiction, and heart failure. Her current drugs include lisinopril, carvedilol, furosemide, insulin, and methadone. **Which one of the following is the best option for initial management of this patient's pain?**
- A. Pregabalin 50 mg orally three times/day.
 - B. Phenytoin 100 mg orally three times/day.
 - C. Carbamazepine 100 mg orally daily.
 - D. Duloxetine 60 mg orally daily.
15. A 45-year-old pharmacist suffers from degenerative joint disease. He says that he used cocaine in the remote past and had two driving while intoxicated convictions about 10 years ago. His family history is positive for alcoholism. He has occasionally used prescribed opioids appropriately for acute pain. His chronic pain has not responded to acupuncture, herbal remedies, or nonsteroidal anti-inflammatory drugs. **Which one of the following would best minimize addiction risk if added to this patient's treatment plan?**
- A. Use of a patient contract.
 - B. Use of less-potent opioid agents.
 - C. Involvement in a 12-step support group.
 - D. Enrollment in a pharmacist recovery network.

16. Your co-worker, a 27-year-old pharmacist, has suffered chronic pain since a motor vehicle crash 3 years ago. She wears a fentanyl patch, and her pain is well controlled. Recently, she was observed stealing several hundred hydrocodone tablets. When confronted, she explained that hydrocodone gives her the energy she requires to complete the demand of working 12-hour days in a high-volume retail pharmacy. **To best address the interests of both the pharmacist and patient safety, which one of the following should you first inform of her hydrocodone hoarding behavior?**
- A. Fentanyl patch prescriber.
 - B. State board of pharmacy.
 - C. Drug Enforcement Agency.
 - D. Pharmacy's employee assistance program.
17. A 63-year-old man presents to the family medicine clinic complaining of burning and tingling in his extremities, inability to sleep at night, and a feeling of hopelessness. He also reports a 20-pound weight gain over the past 6 months, and lack of ability to concentrate. His medical history includes chronic obstructive pulmonary disease, gastroesophageal reflux disease, and alcoholism (heavy consumption for 20 years; in recovery for 15 years). **Which one of the following is the best choice for initial management of this patient's pain?**
- A. Tramadol.
 - B. Duloxetine.
 - C. Clonazepam.
 - D. Pregabalin.
18. A 59-year-old woman presents to her primary care practitioner complaining of a burning sensation in her feet. Her medical history includes type 2 diabetes mellitus, hypertension, myocardial infarction, depression, and anxiety. All of her conditions are well controlled with her current treatment regimens. She has a remote history of opioid abuse. Her current drugs include atenolol, lisinopril, hydrochlorothiazide, and citalopram. **Which one of the following is the best choice for initial pain management in this patient?**
- A. Amitriptyline.
 - B. Venlafaxine.
 - C. Tramadol.
 - D. Lidocaine 5% patch.
19. A 46-year-old woman suffers from diabetic neuropathy, depression, anxiety, and alcohol dependence. She is an alcoholic and has been in remission for 5 years. Her home drugs include metformin, amitriptyline, and buspirone. Amitriptyline monotherapy
- of this woman's diabetic neuropathy has been moderately successful, resulting in an assessed level of pain of 5/10. This pain level is unacceptable to her because it interferes with her ability to stand on her feet to do her job. **Which one of the following agents would be best to add to her therapy to improve control of this patient's pain?**
- A. Capsaicin cream.
 - B. Duloxetine.
 - C. Tramadol.
 - D. Mexelitine.
20. A 39-year-old man has peripheral neuropathy, alcohol addiction, gastritis, gastroesophageal reflux disease, anxiety, depression, anemia, and thrombocytopenia. He underwent a trial of gabapentin for neuropathic pain, but discontinued it after 10 days when he "couldn't feel any difference" and "felt zonked out all the time." During a recent hospitalization, he experienced pronounced pain relief from intravenous lidocaine. **Which one of the following would be best to try next to manage this patient's neuropathic pain?**
- A. Carbamazepine.
 - B. Amitriptyline.
 - C. Pregabalin.
 - D. Mexiletine.