A Pharmacist’s Guide to the Clinical Assessment and Management of Pain

A Continuing Education Monograph for Pharmacists

American Pharmacists Association
Improving medication use. Advancing patient care.
LEARNING OBJECTIVES
After reading this monograph, pharmacists should be able to:

1. Discuss the pathophysiology and etiology of different types of pain and their prevalence.
2. Explain the economic, clinical, and humanistic impact of pain.
3. Discuss the appropriate assessment and diagnosis of pain.
4. Describe appropriate pharmacologic and nonpharmacologic strategies for managing various types of pain.
5. Explain how to convert opioid dosages between medications and routes of administration.
6. Discuss pharmacotherapeutic considerations for special patient populations, including patients with renal, hepatic, or other conditions.

Introduction

Pain is a ubiquitous part of life. The painful experience can be a mild, temporary annoyance that does not interfere with everyday life; it can be excruciating, persist for years, and completely destroy the fabric of the lives of those whom it affects; or it can be anywhere in between. Pain is the most common symptom prompting patients to visit primary care providers, and more than 80% of patients who visit physicians report pain. Although medical advances now allow for adequate management in most affected individuals, pain often remains undertreated.

The undertreatment of pain results from many societal factors, including generalized perceptions that pain is simply something you have to live with, or that pain builds character, and systemic factors such as a sparse number of health care professionals who specialize in the management of pain. The impact of these factors is magnified by the fact that some of the most effective analgesics are common targets of drug misuse and diversion. Concerns about the misuse of these drugs often cloud appropriate management of patients with pain. While these issues are obviously quite salient to pain management activities, this monograph will focus primarily on clinical issues related to pain management.

Pharmacists’ roles in managing pain vary widely. In some cases, pharmacists provide brief patient counseling when patients fill prescriptions at community pharmacies. In others, pharmacists are intimately involved in the assessment, management, and pharmacotherapy of patients with pain. Each pharmacist’s clinical environment will determine the degree of involvement in the patient’s care. However, even pharmacists who have more cursory interactions with patients can assist their patients by helping them understand the appropriate use of the medication and periodically assessing them to ensure that pain management goals are being adequately met.

Understanding Pain

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

As this definition implies, pain is always a subjective experience. While tissue damage usually results in pain, and physical pain is always associated with some part of the body, the fact that pain also must be unpleasant emotionally confers the subjective component. In some instances, severe tissue damage can occur without the individual immediately experiencing pain. This often happens during acute trauma or when an individual is in “fight or flight” mode, which may occur with trauma or battlefield injuries. In other cases, an individual experiences pain without any apparent underlying physiologic cause. Patients who experience allodynia (which can be a component of many different painful conditions) report pain following what would not normally be a painful stimulus. For example, allodynia occurs when a patient with sunburn experiences severe burning pain when clothing rubs across the burn, even though this normally would not be a painful experience. Definitions of
several common pain terms are provided in Table 1.

There is substantial variability in the intensity of pain reported by individuals who are subjected to the same noxious stimuli. This individual variability contributes in part to the perception that some individuals are stoic or brave, while others are perceived as whiners or hypochondriacs.

The patient’s subjective report of pain should be considered the most reliable indicator of the nature and severity of pain. A handful of studies have demonstrated that variability in the subjective reports of pain can be directly correlated with the degree of activation of regions of the brain associated with processing pain. Numerous functionally distinct regions of the brain are involved in the perception of pain, including the anterior cingulate cortex, the primary somatosensory cortex, and the prefrontal cortex. Increasing the intensity of a painful stimulus increases the activity in these brain regions.

In one study of healthy adult subjects, subject ratings of the pain produced by identical noxious stimuli ranged from 1.05 to 8.9 on a 10-point visual analog scale. Brain scans showed significantly greater activity in regions associated with perception of pain intensity (the anterior cingulate cortex, the primary somatosensory cortex, and the prefrontal cortex) in subjects who were highly sensitive to the pain, compared with those who had the least sensitivity. Individuals with similar patterns of activation in these brain regions provided similar subjective reports of pain intensity.

These findings provide validity for patients’ variable subjective reports of the intensity of pain, even when these reports appear to be greater than one would expect. Interestingly, recent studies in patients with chronic painful conditions, including fibromyalgia and irritable bowel syndrome, have shown increased activation in these brain regions compared with controls. This research indicates that such patients experience certain painful conditions more intensely than unaffected individuals do. In other words, patients who report different intensities of pain from similar clinical conditions actually are experiencing the pain differently.

### Types of Pain

Many classification systems are used to describe the different types of pain. The most common classification schemes refer to pain as either acute or chronic; malignant or nonmalignant; and somatic, neuropathic, or visceral.

The difference between acute pain and chronic pain refers to the duration of the pain, but there are many more important distinctions between these two classifications (Table 2). Historically, acute pain was considered to be pain that lasted less than 3 months and chronic pain was that lasting longer. However, this 3-month cut-off is arbitrary and does not have a meaningful relationship to the time course of many pain conditions. A more appropriate distinction is that acute pain serves an important physiologic purpose that warns of tissue damage or the potential for further injury, and serves a protective purpose. Acute pain is normally present following injury or surgery and generally subsides as healing occurs and pain-producing stimuli diminish.

Chronic pain is pain that has outlived its usefulness. Chronic pain does not relate to an injury or provide physiologic value. Chronic pain continues beyond the expected time frame for healing and can be a disease in its own right.

The term “malignant pain” has historically been used to refer to pain resulting from cancer—either pain caused by tumors themselves or pain caused by treatments such as chemotherapy, radiation, or surgery. However, a newer definition for malignant pain is pain that is “associated with progressive disease that is potentially life limiting.” This definition includes pain resulting from conditions such as acquired immunodeficiency syndrome (AIDS), progressive neurologic diseases, end-stage organ failure, and dementia.

Using this definition, chronic nonmalignant pain is that which results from disorders that are not life threatening. In conditions such as arthritis, pain results from ongoing tissue damage, while in other conditions, such as reflex sympathetic dystrophy, pain results from abnormal activity of pain receptors. Nociceptive pain includes both somatic pain and visceral pain. Somatic pain is that which arises from the skin, bone, joint, or muscle and is usually experienced as discomfort or pain. Visceral pain results from damage to internal organs or tissues and is often described as deep, dull, or aching.

### Table 1. IASP Definitions of Selected Pain Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Meaning</th>
</tr>
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<tbody>
<tr>
<td>Allodynia</td>
<td>Pain that results from a stimulus that does not normally cause pain</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Absence of pain from a stimulus that would normally cause pain</td>
</tr>
<tr>
<td>Causalgia</td>
<td>Persistent burning pain, allodynia, and hyperpathia following a traumatic nerve lesion</td>
</tr>
<tr>
<td>Central pain</td>
<td>Pain that results from a lesion or dysfunction in the central nervous system</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>An unpleasant abnormal sensation</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>An increased pain response to a stimulus that normally causes pain</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>Pain in the distribution of a nerve or nerves</td>
</tr>
<tr>
<td>Neuritis</td>
<td>Inflammation of a nerve or nerves</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>Pain resulting from a lesion or dysfunction of the nervous system</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>An abnormal (but not unpleasant) sensation*</td>
</tr>
</tbody>
</table>

*Note: IASP defines the sensation as a dysesthesia if it is considered unpleasant.

IASP = International Association for the Study of Pain.

Source: Reference 2.
Acute vs. Chronic Pain

MECHANISMS OF PAIN

Pain can result from multiple physiologic pathways. The type of injury a patient has can affect the type of pain the patient experiences. Nociceptive pain is different mechanistically from neuropathic pain. Nociceptive pain is mediated at nociceptors that are widely distributed in cutaneous tissue, bone, muscle, connective tissue, vessels, and viscera. These nociceptors are classified as thermal, chemical, and mechanical-thermal, based on the types of sensations that they transmit. Patients typically use terms such as sharp, dull, achng, or throbbing to describe nociceptive pain. Examples of nociceptive pain include postsurgical pain, bone pain, and pain due to trauma.

Neuropathic pain is elicited by damage to or pathologic changes in the peripheral or central nervous system (CNS). Neuropathic pain often is described in terms such as burning, tingling, shooting, or electrical. Examples of neuropathic pain include postherpetic neuralgia, trigeminal neuralgia, peripheral and traumatic neuropathies, and complex regional pain syndrome.

The mechanisms of nociceptive pain are the most well defined and provide a framework for understanding the mechanisms of other types of pain. The pathophysiology of nociceptive pain involves the transduction of noxious stimuli in the periphery, the transmission of these stimuli to the CNS, the conscious perception of pain, and modulation of these systems.

Free nerve endings located in skin, muscle, and the viscera that perceive pain signals are called nociceptors. Transduction is the reception of noxious impulses and initiation of action potentials at nociceptors. These nociceptors can be activated by various stimuli that result in tissue injury. Tissue injury causes the release of bradykinin, serotonin, potassium ions, and histamine, and triggers the release of prostaglandins and substance P, which increase the sensitivity of the nociceptors but do not stimulate them directly.

During transmission, afferent nerve fibers from nociceptors (including fast, myelinated type A-delta fibers and slower, unmyelinated type C fibers) transmit action potentials to the spinal cord and then the brain (Figure 1). Fast, sharp, well-localized pain signals are transmitted along the myelinated A-delta fibers, while C fibers transmit dull, achng, poorly localized pain. The afferent nerve fibers synapse in the dorsal horn of the spinal cord, where they release a number of neurotransmitters, including glutamate, substance P, and calcitonin gene-related peptide. These neurotransmitters trigger the continuing transmission of pain signals through various ascending pathways in the spinal cord to the thalamus (often referred to as the relay center) in the brain stem. From the thalamus, pain is transmitted to higher cortical regions, where it is processed and perceived as pain.

Several factors can modulate the perception of pain. Other sensory input from the periphery travels along the same pathways as nociceptive input. Because the brain can process only a limited number of signals, nonnoxious input can alter the perception of pain. According to the gate-control theory, transmission of afferent pain signals from the periphery to the spinal cord and brain may be modulated by mildly stimulating the type A-delta fibers, which reduces the transmission of pain signals by type C fibers. Other psychological techniques such as relaxation, distraction, and guided mental imagery also can decrease pain in part through limiting the number of pain signals that are processed in the cortex.

Table 2. | Acute vs. Chronic Pain

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute Pain</th>
<th>Chronic Nonmalignant Pain</th>
<th>Chronic Malignant Pain*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Hours to weeks, depending on cause</td>
<td>Months to years</td>
<td>Unpredictable</td>
</tr>
<tr>
<td>Pathology</td>
<td>Present</td>
<td>Often little or none</td>
<td>Usually present</td>
</tr>
<tr>
<td>Examples of causes</td>
<td>Surgery, Trauma, Medical procedures</td>
<td>Ongoing tissue injury (e.g., arthritis) Back pain (with or without associated pathology)</td>
<td>Headache Cancer or cancer treatments Acquired immunodeficiency syndrome Congestive heart failure Multiple sclerosis</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Predictable</td>
<td>Unpredictable</td>
<td>Increasing pain with the possibility of disfigurement or death</td>
</tr>
<tr>
<td>Complicating issues and psychosocial effects</td>
<td>Uncommon</td>
<td>Profound complications including depression, anxiety, and financial issues</td>
<td>Usually profound, including loss of control, issues of confronting one’s mortality</td>
</tr>
<tr>
<td>Nerve conduction</td>
<td>Rapid</td>
<td>Slow</td>
<td>Slow</td>
</tr>
<tr>
<td>Autonomic nervous system involvement</td>
<td>Present</td>
<td>Generally absent</td>
<td>Present or absent</td>
</tr>
<tr>
<td>Biologic value</td>
<td>High</td>
<td>Low or absent</td>
<td>Low</td>
</tr>
<tr>
<td>Treatment</td>
<td>Primarily analgesics</td>
<td>Multimodal</td>
<td>Multimodal</td>
</tr>
</tbody>
</table>

*Defined as pain resulting from any progressive, potentially life-threatening disease.

Source: Reference 6.
During modulation, the perception of pain is moderated by inhibitory pathways descending from the thalamus and brain stem. The endogenous opiate system uses endorphins (enkephalins, dynorphins, and beta-endorphins) that interact with mu, delta, and kappa opioid receptors throughout the CNS. These endorphins bind to the opioid receptor sites to inhibit transmission of pain impulses or to alter perception. Stimulation of N-methyl-D-aspartate (NMDA) receptors located in the dorsal horn can decrease the mu-receptor response to opioids. Antagonism of NMDA receptors reverses this effect. Other important neurotransmitters that inhibit the transmission of pain include serotonin, norepinephrine, gamma-aminobutyric acid (GABA), and neuropeptide-Y.9

Ongoing nociceptive input from the periphery can produce central sensitization to pain, referred to as the “wind-up” phenomenon.14 Prolonged input from C fibers leads to longer-lasting responsiveness in the dorsal horn. Activation of the NMDA receptors appears to play a prominent role in this process. The increase in excitability in the dorsal horn can then last for minutes or hours longer than the initial noxious stimuli. This central sensitization can result in recruitment of neurons that are not normally involved in transmitting pain, leading to hyperalgesia, allodynia, and/or the spread of pain to uninjured tissues.15 In neuropathic pain, nerve damage or persistent stimulation can result in pain circuits rerouting themselves to produce continual nerve stimulation. The wind-up phenomenon explains observations that untreated acute pain can lead to the development of chronic pain, and that the longer pain goes untreated, the harder it becomes to treat.

PAIN AND QUALITY OF LIFE

Chronic pain affects almost every aspect of a patient’s life—physical, mental, social, financial, and spiritual. All these factors together combine to produce the actual degree of suffering experienced by the patient. Unrelieved pain can produce a variety of harmful physiologic effects. Examples of these effects are listed in Table 3.15 Untreated pain can alter neurotransmission signals, modulate pain pathways, and make it more difficult to treat pain in the future. In the acute setting, these effects can delay recovery and contribute to the development of a chronic pain condition. In addition, poorly managed pain can impair a patient’s ability to achieve restful sleep, impairing concentration and cognitive abilities and making the patient irritable. This can become a vicious cycle in that lack of sleep makes patients more sensitive to pain and can exacerbate the negative psychological effects of pain.

Negative psychological effects associated with unrelieved pain include the development of feelings of anger, fear, resentment, depression, and anxiety. Many patients report a loss of enjoyment of life, feelings of social isolation, an inability to relate to others, and conflicts in interpersonal relationships. Many patients with chronic pain contemplate suicide and some attempt it. Social and psychological experiences can alter a patient’s experience of pain. Individuals with chronic pain are more likely to develop depression if they have low levels of confidence in their abilities to manage pain, cope, and function. Furthermore, the presence of depression when an acute injury occurs is a predictor for the development of chronic pain.16

Patients also may be frustrated and angry with their pain, the health care system, and employers or insurers. Anger and frustration can further exacerbate the pain condition—in one study, anger and hostility were found to be closely associated with the degree of pain that patients reported.17 Chronic pain also can have a drastic impact on a patient’s ability to function. In one survey of chronic pain patients, 13% reported that their pain required them to obtain assistance in their activities of daily living and 13% reported that they had moved to a different residence that was easier to manage because of their pain.18 Pain also can interfere with function in less profound ways. Many patients may not be able to participate in sports or leisure activities that had previously been a source of enjoyment. Patients may limit their socialization because activities like dancing or a night out with friends may be impossible. Even what seems like a simple activity such as going to a movie may be excruciating for patients who have back pain and cannot sit for extended periods. Patients may find themselves limited in their ability to interact with their children or grandchildren, which may be a significant source of suffering. They also may feel as though they have become a burden on other family members as a result of both caregiving and financial responsibilities. Many patients find that their interpersonal relationships deteriorate as a result of their condition, and their social circle dwindles, leaving them feeling even more isolated and alienated. With diminishing social circles, patients may find themselves even less able to cope with the pain and the limitations it causes. Pain may prevent patients from achieving various personal and professional life goals.

Many patients with chronic pain are unable to maintain gainful employment, or are underemployed. In one survey, more than 25% of respondents with chronic pain stated that their condition affected their decision to quit their job.19 In another survey of patients with chronic pain, 20% reported taking disability leave from work and 17% reported that they had to change jobs altogether.18 Spiritually, many patients who suffer from chronic pain may question their beliefs about God, or feel that God is punishing them for real or perceived transgressions. Patients may go through a period of mourning for their former selves. For patients with malignant disease, pain may be perceived as a signal of disease progression and impending death.
The multifaceted nature of suffering associated with chronic pain makes it particularly difficult to treat. All of the various aspects of suffering must be considered when assessing and treating patients with pain.

**PREVALENCE OF PAIN**

Identifying the prevalence of pain is a complex task. Virtually all people experience pain at some point, and pain is a symptom of many diseases. According to the American Pain Foundation, more than 50 million persons in the United States suffer from chronic pain caused by various diseases and disorders each year, and an additional 25 million experience acute pain resulting from injuries or surgery.20 Other statistics show that chronic pain affects about 20% of the adult population, and is more prevalent in women and the elderly.21 The most common forms of chronic pain are back pain, headache, and joint pain.

Frequent back pain reportedly affects 26 million people between 20 and 64 years of age.22 Migraines affect more than 25 million Americans, and fully 90% of Americans report nonmigraine headaches each year.24 Approximately 4 million suffer from fibromyalgia.24 Cancer is commonly associated with pain (hence the distinction between “cancer pain” and “noncancer pain”). Nearly 1.4 million Americans will be diagnosed with cancer in 2004, and about 70% will experience significant pain resulting from their illness.25,26 One survey found that 43% of Americans report that pain frequently affects their participation in activities.24

Reading these statistics, it seems that almost everyone is in pain. Obviously, not everyone who experiences pain is debilitated by it. For some, pain is mild or moderate and intermittent, rarely interfering with daily activities or easily managed with self-care treatments. For others, pain is severe and disabling, completely takes over their lives, and requires multidisciplinary care to help them manage their pain.

Other indices provide a more general picture of the impact of pain. While exact numbers are hard to pinpoint, there is little doubt that pain is very expensive for our economy. A number of different estimates have attempted to quantify the cost of pain in the United States. For back pain alone, the 1988 National Health Interview Survey found that there were 149.1 million lost work days each year, equivalent to $14 billion in lost wages. (This estimate does not account for costs associated with the treatment of back pain.) The National Institute for Occupational Safety and Health estimated that, in 1990, the cost to society from low back pain was between $50 billion and $100 billion per year.27 If the medical costs, sick days, disability payments, and lost productivity were added for all painful conditions that prevent patients from working, the cost would be far greater.

The American Productivity Audit, a survey of the U.S. workforce conducted from 2001 through 2002, found that the lost productivity time due to arthritis, back pain, headache, and other musculoskeletal pain is approximately $80 billion per year.28

The Assessment of Pain

Even though pain is a common presenting complaint in health care, lack of regular assessment and reassessment of pain remains widespread and contributes to the undertreatment of pain.29 Perhaps because there are no reliable objective markers for pain, there is much confusion about appropriate assessment

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**Table 3. | Examples of Physiologic Effects of Unrelieved Pain**

<table>
<thead>
<tr>
<th>System</th>
<th>Responses to Pain</th>
<th>Examples of Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine/metabolic</td>
<td>Metabolic disturbances related to altered release of hormones (e.g., adrenocorticotropic hormone, cortisol, catecholamines, insulin)</td>
<td>Weight loss, Fever, ↑ Respiratory rate, ↑ Heart rate, Shock</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>↑ Heart rate, ↑ Vascular resistance, ↑ Blood pressure, ↑ Myocardial oxygen demand, ↑ Hypercoagulation</td>
<td>Unstable angina, Myocardial Infarction, Deep vein thrombosis</td>
</tr>
<tr>
<td>Respiratory</td>
<td>↓ Air flow due to reflex muscle spasm and voluntary “splinting” mechanisms that limit respiratory effort</td>
<td>Atelectasis (incomplete expansion of the lung), Pneumonia</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>↓ Rate of gastric emptying, ↓ Intestinal motility</td>
<td>Delayed gastric emptying, Constipation, Anorexia, Ileus</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Muscle spasm, Impaired mobility and function</td>
<td>Immobility, Weakness, Fatigue</td>
</tr>
<tr>
<td>Immune</td>
<td>Impaired immune function</td>
<td>Infection</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Abnormal release of hormones that affect urine output, fluid volume, and electrolyte balance</td>
<td>↓ Urine output, Hypertension (fluid retention), Electrolyte disturbances</td>
</tr>
</tbody>
</table>

Source: Reference 15.
A thorough assessment of pain should include questions about pain, pain relief, and assessment of current treatment for appropriateness, efficacy, and adverse events. Questions to ask about pain include those relating to onset, duration, location(s), quality, severity, and intensity. The patient should be questioned about the duration and predictability of the pain, as well as what alleviates or exacerbates it. The patient assessment also should consider the impact of pain on patient function, behavior, and psychological state.

Another common mnemonic for the assessment of pain is PQRST. Using this system, the patient is asked about the following:

- **P**rove or palliate: What makes the pain better or worse?
- **Q**uality: What does the pain feel like? Is it sharp, dull, stabbing, burning?
- **R**adiation: Does the pain radiate, and where to?
- **S**everity: How severe is the pain?
- **T**ime: When did the pain start, and how long has it lasted?
- **U** (you): What is the impact of pain on you? 

A detailed patient interview regarding the nature and impact of the pain is an important part of pain assessment. The clinician should both look at the pain itself and attempt to diagnose the underlying condition causing the pain. A comprehensive history can lead to improved management of pain by providing insights about which treatments might be most effective. In addition to the description of pain, the patient history should include a general medical history, family and psychosocial history, a functional assessment, and a discussion of the patient’s goals and expectations.

Many tools designed specifically for assessing the severity of pain have been developed, including rating scales and multidimensional tools. Rating scales provide a simple tool for obtaining the patient’s report of pain intensity.
Numeric scales are widely used by asking patients to rate their pain on a scale of 0 to 10, with 0 signifying no pain and 10 indicating the worst pain imaginable. Using such a scale, a rating of 1 to 3 is generally considered mild pain, 4 to 7 is moderate pain, and 8 to 10 is severe pain. Some patients may have initial difficulty assigning a number to their pain and might benefit more from the use of other unidimensional scales. Patients should be questioned about their level of pain at the time of the assessment, and the worst degree of pain that they have experienced with the complaint in question.

A visual analog scale is similar to a 0 to 10 rating scale in that patients are required to place a mark on a line that is 10 cm long with “no pain” marked on one end and “worst possible pain” marked on the other. The clinician then measures where the patient’s mark is on the line to generate a pain intensity score between 0 and 10.

Categorical scales allow patients to select from among various options to describe their pain. Such options may be a list of words or pictures of faces. For example, the Wong-Baker FACES Pain Rating Scale can be used to help patients communicate how much pain they are experiencing (Figure 2). Such scales may be particularly helpful for assessing pain in children or in cognitively impaired individuals.

Multidimensional assessment tools also obtain information about the nature of the pain and its effects on the patient’s quality of life. Although such tools provide additional important information about the nature of the pain, they are more complex and time consuming to use than unidimensional tools and are not used as frequently. Their use also is limited by the cognitive abilities of the patient and language barriers. Such tools include the Initial Pain Assessment Tool, the Brief Pain Inventory, and the McGill Pain Questionnaire. Internet links to these patient assessment tools are provided in the Appendix. Such tools include questions about various aspects of pain and the effect of the pain on the patient’s life. The Neuropathic Pain Scale was developed specifically to assess patients who have neuropathic pain. This scale is designed to assess distinct pain qualities associated with neuropathic pain.

The Oswestry Disability Index assesses the degree to which a patient’s function is affected by pain. This assessment tool was originally developed to assess the functional impact of low back pain, but also can be used more broadly. It asks questions about the impact of the pain on lifting, walking, sitting, standing, sleeping, traveling, patients’ social life, and patients’ ability to wash and dress themselves.

In addition to these assessments, the open interview should ask questions about other limitations that are created by the pain. For example, some patients may find limitations in their ability to participate in hobbies to be especially frustrating. Others may be most bothered by the pain’s impact on their ability to interact with and care for family members. An increase in functional capacity is an important outcome for pain manage-

### Table 5. Information That Should Be Assessed During a Pain History

<table>
<thead>
<tr>
<th>Factors Assessed</th>
<th>Types of Information to Obtain</th>
</tr>
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<tbody>
<tr>
<td>Nature of pain</td>
<td>Onset and duration&lt;br&gt;Location(s) and radiation, if any&lt;br&gt;Quality&lt;br&gt;Intensity&lt;br&gt;Associated symptoms&lt;br&gt;Factors that exacerbate or alleviate pain, including medical interventions</td>
</tr>
<tr>
<td>Attempted management strategies</td>
<td>Ask about current and prior attempts to manage the pain. For prior attempts, ascertain why intervention was discontinued.&lt;br&gt;Medications (prescription, nonprescription, supplements)&lt;br&gt;Nonpharmacologic treatments (physical therapy, etc.)&lt;br&gt;Complementary and alternative treatments (chiropractic, acupuncture)&lt;br&gt;Other coping strategies (distraction, prayer)</td>
</tr>
<tr>
<td>Medical history</td>
<td>Prior and coexisting illnesses (including mental comorbidities, substance abuse disorders)&lt;br&gt;History of accidents and surgeries</td>
</tr>
<tr>
<td>Family history</td>
<td>Health status of family members&lt;br&gt;Family history of pain or illness, including depression (a family history of depression increases the likelihood of depression in pain patients)</td>
</tr>
<tr>
<td>Psychosocial history</td>
<td>Developmental, marital, or vocational problems&lt;br&gt;Stressors or depressive symptoms&lt;br&gt;Compensation/litigation issues</td>
</tr>
<tr>
<td>Functional impact of pain</td>
<td>Impact of pain on the patient’s: Work&lt;br&gt;Other daily activities (e.g., ability to care for house and family members, ability to participate in sports or hobbies)&lt;br&gt;Personal relationships&lt;br&gt;Sleep, appetite, emotions</td>
</tr>
<tr>
<td>Expectations and goals</td>
<td>What the patient hopes to achieve with regard to: Intensity of pain&lt;br&gt;Functional abilities&lt;br&gt;Quality of life</td>
</tr>
</tbody>
</table>

*Source: Reference 15.*
General physical condition.

hurts a little

Explain to the person that each hurts just a little bit.
hurts even more.
The Wong-Baker FACES hurts as much as you can imagine,
Pediatr

Range of motion.
Point to each face, using the Musculoskeletal and neurologic systems.

This phenomenon helps to explain why some patients with chronic pain rate their pain very highly without showing any outward signs of distress.

Comorbid conditions also should be considered when assessing the patient with pain. Renal and hepatic function are important parameters that can affect medication selection and dosing. Controlling comorbid conditions such as diabetes may have an impact on the progression of neuropathic pain in affected patients. Issues that could affect bowel function are also important. Other medications used by the patient also should be documented, because these can have important implications for medication selection if the patient is a candidate for pharmacologic treatment.

Evaluation of the patient’s psychological status is important, particularly for patients with chronic pain. Depression is common in this population, and affects up to 50% of patients with chronic pain.34 In addition, patients with depression are more likely to have comorbid chronic pain than the general population.35

Finally, the patient’s history of drug and alcohol abuse should be explored. Given that about 50 million people in the United States have chronic pain, and that 3% to 16% of the population suffers from an addictive disorder (including addiction to alcohol but not to nicotine), it is reasonable to conclude that millions of patients suffer from both chronic pain and addiction.36 Special precautions must be implemented if opioids or other medications with a potential for abuse are used to treat patients with a history of an addictive disorder. In addition, health care providers must take care to be alert for patients with addictive disorders who are posing as pain patients to obtain desired medications. Additional information about appropriate precautions to take with regard to addictive disorders can be found in the Special Populations section and in the resources listed in the Appendix.

Diagnosis in Pain Management

Pain can be produced by thousands of different medical conditions, each with its own specific pathophysiology. For example, there are more than 100 different forms of arthritis, and headaches can be classified into more than 100 categories.24,37 In some cases, no physiologic cause for the pain can be identified. If clinicians are unable to discover the cause of the pain and provide a definitive diagnosis, this does not mean that the patient is not experiencing pain. Chronic pain can be a disease in and of itself.

Identifying the source of pain through objective and subjective evaluation is important because it can help guide selection of curative agents and therapies if available, or disease-specific agents. For example, the triptans are particularly useful for treating migraine headaches, and several medications are specific to treating rheumatoid arthritis. Such agents have no effect on treatment of conditions that result from differing pathophysiology (e.g., cluster headaches, osteoarthritis). Because of the heterogeneity of different painful disorders, it is not possible to review all medications that are used for treating painful conditions. This report will focus primarily on treatments that have general analgesic effects. However, pharmacists should keep in mind that disease-specific treatments also may benefit their patients.

All patients with a pain complaint should have a physical examination to identify the underlying cause(s) of the pain, if possible. The physical exam should include evaluations of the following:

- General physical condition.
- Musculoskeletal and neurologic systems.
- Range of motion.
- Effect of physical factors on pain and performance measures.

Identifying whether the pain is nociceptive or neuropathic in nature also is important, particularly for selection of adjuvant pharmacologic agents.

Diagnostic tests may be used to supplement the physical exam if the health care provider feels that they are appropriate. Such tests can assist the diagnosis and lead to selection of management strategies with improved outcomes. However, in some cases, diagnostic tests provide little information of value and are not appropriate. For example, most patients with acute low back pain do not require imaging studies unless red flags for more
serious conditions are present.\textsuperscript{38,39} Imaging studies are costly and do little to assist the diagnosis or treatment of the majority of patients with this condition. In addition, imaging studies often are inconclusive, and abnormalities that may be seen do not correlate well with the amount of pain the patient experiences. Normal degenerative changes associated with age could be mistaken as the cause of acute low back pain—up to 30\% of individuals over 30 years of age without symptoms have false-positive diagnostic findings with imaging studies such as computed tomography and magnetic resonance imaging.\textsuperscript{39} The rationale for not performing such tests should be explained to patients, because they may expect to undergo imaging studies and receive a more precise diagnosis.\textsuperscript{40}

Management of the underlying disease should not preclude treatment of pain. Pain management should be provided simultaneously with other interventions. As discussed earlier, poorly managed pain can actually impair healing. Thus, pain treatment may contribute to better management of the underlying clinical condition.

**Treatment of Pain**

Treatment of pain involves nonpharmacologic and pharmacologic modalities. Acute pain usually is managed through the use of analgesics and other straightforward interventions (e.g., ice, heat). Chronic pain, on the other hand, affects the whole person and requires a multimodal approach to address the multiple dimensions of the person’s suffering, including physical, psychological, and behavioral issues that are related to the patient’s disability. This is the preferred approach to the treatment of chronic pain.

Goals of treatment should be established when initiating a treatment regimen. Prevention, reduction, or elimination of pain is an important therapeutic goal. Functional impairments that are identified during the patient assessment also can play an important role in goal setting. The patient should be involved in the establishment of these goals so that outcomes important to the patient are incorporated into the treatment goals and so that patients have realistic expectations. Particularly in patients with chronic pain, it is likely that pain will not be completely eliminated, but must be managed. Additional important goals include improving the patient’s quality of life, functional capacity, and ability to retain (or regain) independence. Each patient should have specific therapeutic goals established. For example, a patient’s goals might include the following:

1. Pain ≤ 3 at rest.
2. Pain ≤ 5 with movement.
3. Able to have at least 6 hours of sleep uninterrupted by pain.
4. Able to garden for 1 hour.

Depending on the nature of the pain complaint, treatment may involve pharmacologic or nonpharmacologic approaches, or both. However, there is no “one size fits all” approach to pain management. Individual patients respond quite differently to medications and nonpharmacologic treatments. If one attempted therapy proves unsuccessful or produces intolerable adverse events, multiple other approaches are available that may benefit the patient.

Pharmacologic management of pain should be only one component of the overall approach to pain management. A variety of treatment modalities, including physical, psychological, complementary, and invasive treatments, should be considered. Treatments should be individually tailored based on frequent and careful evaluation of the patient’s response.

**Interdisciplinary Approaches**

For mild to moderate, self-limiting pain, pharmacists may be the only providers needed to guide appropriate self-care practices. Severe acute pain often can be managed by a primary care provider or pharmacist. Following surgery, many anesthesiologists and pharmacists are solely responsible for managing pain. However, because chronic pain and associated comorbidities present a much more complex biopsychosocial problem, a multidisciplinary approach often is needed. Members of the multidisciplinary team may include physicians, pharmacists, social workers, anesthesiologists, nurses, psychologists, psychiatrists, physical therapists, religious leaders, and others.

**Palliative Care and Hospice Programs**

Palliative care and hospice programs are specialized pain and symptom management programs. Although the terms often overlap in common usage, palliative care is not synonymous with end-of-life care, and can be provided to patients who are not terminally ill. Palliative care focuses on the prevention and relief of suffering, with particular emphasis on the emotional, spiritual, and practical needs of patients. Palliative care should be available at any time during a serious illness and should not be reserved for patients who have no hope of recovery.

Hospice care is specific to patients who are approaching the end of life. In order to receive hospice care, a physician has to certify that a patient’s life expectancy is 6 months or less, and both patient and physician must agree to forgo further treatments directed at prolonging life. Hospice care emphasizes enhancing the quality of life and preserving the patient’s sense of dignity and self-worth, and also assists loved ones in adjusting to the patient’s illness and death.

**Ethical Issues in Pain Management**

**Barriers to Pain Management**

Barriers to optimal pain management sometimes arise as a result of the knowledge and beliefs of health care providers. Some clinicians do not think of pain relief as an important goal. Others may not completely believe their patient’s reports of the severity of the pain. In addition, some providers may believe that patients are intentionally exaggerating their symptoms. Poor clinical knowledge about available pain management strategies, including pharmacologic, nonpharmacologic, and alternative treatment options, combined with exaggerated concerns about the risk of opioid misuse and diversion, also contribute to suboptimal provider treatment of pain.\textsuperscript{15} Some health care providers have become overly wary due to experiences with patients who have abused medications. Misperceptions about the distinctions among addiction, physical dependence, and tolerance, as well as a failure to recognize pseudoaddiction, also can impede pain management. These terms are defined in Table 6.\textsuperscript{41}

Physical dependence is defined as the occurrence of withdrawal syndrome when stopping or quickly decreasing opioids. It should be stressed that this is normal and is not an indicator of addiction.

Addiction is defined as psychological dependence on the use of substances and is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.\textsuperscript{42} Addiction should be considered if these features are present. An important distinction between addiction and appropriate use is that addicted individuals experience a loss of function, while
increased dosage should reduce or eliminate the inappropriate behaviors. If the person is seeking opioids for illicit purposes, an increased dosage will not diminish the aberrant behaviors.

Patients also may present barriers to pain management. Some patients have cultural beliefs that dictate that pain should not be reported. Others may be reluctant to use opioids as a result of fear of addiction or the stigma associated with these medications. Systemic factors that can hinder pain management include lack of regular assessment, regulatory burdens, or lack of payment for pain services.

Use of Placebos
Placebos should never be used in the treatment of pain.43 Use of placebos is deceptive, can harm the patient-provider relationship, and does not provide useful information about the nature of pain. A placebo response has been demonstrated in patients with a documented organic cause of pain. The American Pain Society has declared that the use of placebos is unethical and should be avoided.45

Table 6. Definitions Related to the Use of Opioids for the Treatment of Pain

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction</td>
<td>Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.</td>
</tr>
<tr>
<td>Physical dependence</td>
<td>Physical dependence is a state of adaptation that is manifested by a drug class—specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.</td>
</tr>
<tr>
<td>Tolerance</td>
<td>Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.</td>
</tr>
<tr>
<td>Pseudoaddiction</td>
<td>Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may “clock watch,” and may otherwise seem inappropriately “drug seeking.” Even such behaviors as illicit drug use and deception can occur in the patient’s efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated.</td>
</tr>
</tbody>
</table>

The American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine recognize these definitions and recommend their use.

Source: Reference 41.

Nonpharmacologic Treatment Options for Pain

Nonpharmacologic therapies may be used to manage pain either alone or as adjunctive measures to pharmacotherapy. These therapies include psychological interventions, physical therapy, and complementary and alternative medicine (CAM).

Psychological Interventions
Psychological interventions can play an important role in the management of both acute and chronic pain, can reduce anxiety, and can enhance coping.44 They can help reduce the suffering component of the pain experience, and can reduce anxiety, depression, fear, and anger. These effects result in fewer biologic stress responses and their negative physiologic consequences. These interventions include imagery and distraction, relaxation, biofeedback, contingency management (also called operant conditioning), cognitive behavior therapy, and psychotherapy.15

Techniques such as imagery (e.g., picturing oneself in a safe, peaceful place) and distraction (e.g., listening to music or focusing on breathing) are used to preoccupy patients so that their attention is diverted from the pain. These techniques are particularly useful for procedural and acute pain, but also play an important role in chronic pain management. They can reduce hospital stays, and improve psychological well-being and satisfaction with care.44 Relaxation techniques also serve to decrease the patient’s focus on pain, with the added benefit of reduced autonomic arousal and decreased anxiety.

In biofeedback, the patient is educated to exercise voluntary control of physiologic activities such as heart beat, muscle tension, and skin temperature. The goal is to teach the patient to mentally control physiologic responses to pain. Biofeedback appears most effective for headache, chronic low back pain, and myofascial pain.15
Contingency management is used to help patients change their behaviors by reducing reinforcement for sick-role behaviors and encouraging positive behaviors. For example, patients are praised for exercising and engaging in nonmedical activities. This technique has been shown to effectively reduce chronic pain.13

Cognitive behavioral therapy helps patients modify their perception of pain, increase their sense of control, and decrease maladaptive behaviors. Patients are taught to monitor and evaluate negative thoughts, and manage pain and stress. Psychotherapy is most useful for patients with chronic pain accompanied by psychological comorbidities or maladaptive behaviors. Psychotherapy also may be helpful for patients with malignant disease to assist them in coping with fear of disability, disfigurement, and death.

Educational interventions are designed to provide patients with information about the events that they will likely experience. Such a strategy may help patients to cope with pain, reduce fear, and reduce the subjective component of the pain experience.44

Physical Therapy

Physical therapy is an important component of the pain management program of many patients. Modalities used in physical therapy include heat, cold (cryotherapy), water, sound therapies (e.g., ultrasound), transcutaneous electrical nerve stimulation (TENS), and therapeutic exercise. Such modalities can both decrease pain and improve functioning.

Heat is commonly used in physical therapy in addition to other treatments. Heat produces vasodilation, which results in increased tissue perfusion of oxygen and nutrients, and helps removal of carbon dioxide, metabolic waste products, and pain mediators.13 Heat also relaxes muscles and can decrease muscle spasms. Heat is commonly used in the treatment of muscle spasms, myalgia, fibromyalgia, contractures, collagen vascular disease, and bursitis.

Heat and cold have the ability to reduce pain arising from many different musculoskeletal and neurologic conditions. Acute injuries are usually treated with rest, ice, compression, and elevation (RICE) for the first 24 to 48 hours. Cold decreases metabolism and inflammation, and slows nerve conduction velocity. Direct application of cold results in vasoconstriction, leading to decreased edema and hemorrhage. All these effects combine to produce analgesia.13 Various types of cryotherapy include cold packs, ice massage, cold water immersion, and vapocoolant spray (e.g., ethyl chloride, Fluori-Methane®). Some of these interventions are used for more prolonged periods for certain patients. However, excessive icing should be avoided because it can reduce vascular clearance of inflammatory mediators and further tissue damage. Cryotherapy should be avoided in patients with arterial insufficiency, Raynaud’s disease, cold insensitivity, cryoglobulinemia and paroxysmal cold hemoglobinuria, or allergy (e.g., cold-induced urticaria).13

Heat may be used independently of other physical therapy techniques. Patients with mild to moderate self-limiting sprains and strains, or those with chronic conditions such as arthritis or chronic low back pain, may derive benefit from the application of heat. A variety of heating devices are available, including personal heat therapy wraps or patches (e.g., Thermacare® Therapeutic Heat Wraps) that deliver low-level heat. These nonprescription products contain iron and other natural materials that undergo an exothermic oxidative reaction when exposed to air. Personal heat therapy products are particularly useful for treating low back pain, neck and shoulder pain, wrist pain, and menstrual pain. A study of patients with unspecified low back pain found heat wraps to be significantly more effective than either acetaminophen 4,000 mg/day or ibuprofen 1,200 mg/day for reducing pain, muscle stiffness, and disability scores.45 Another study that compared continuous low-level heat wraps with placebo found similar results.46 The most common adverse effect was skin redness at the site of application.

Heating modalities used in physical therapy may include hot packs, paraffin, heat lamps, hydrotherapy, fluid therapy, or deep-heating modalities such as ultrasound, phonophoresis, and diathermy. Deep-heating modalities are preferred for tissues more than a few centimeters from the surface. Ultrasound is the most commonly used deep-heating modality, and is often used for myofascial pain, contractions, and subacute or chronic inflammation. It also is widely used for sports injuries.13

Phonophoresis uses ultrasound to promote absorption of topical medications, including nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroid creams.

Because of the potential for tissue damage, heat should be avoided in patients with inadequate vascular supply, acute injuries, or reduced sensation (e.g., patients with diabetic neuropathy). Heat also should be avoided in patients with bleeding disorders. Extreme caution should be used if heat is applied to patients with impaired communication or cognitive ability because such patients may not reliably report pain. Malignancy is a relative contraindication to the use of heat; however, factors such as type of malignancy, location, and prognosis for the patient may influence this decision.13

Electric stimulation is another modality often used in physical therapy. TENS is a commonly used electrical modality. TENS takes advantage of the gate theory of pain by using electrodes placed on the skin to stimulate nerve fibers that transmit non-nociceptive information. This electrical stimulation of nerve fibers can compete with and block the pain signal from being transmitted to the brain.47 In addition, some researchers believe that TENS stimulates the endogenous production of endorphins or enkephalins. Some of the analgesia produced by TENS can be reversed by naltrexone, which supports this theory.13 TENS produces analgesia that is similar in magnitude to acetaminophen with codeine.13 This technique may be used in the perioperative period or for the treatment of some painful musculoskeletal conditions.48

Stretching is widely used in physical therapy. It is used to lengthen soft-tissue structures, increase range of motion, and decrease contractions. For example, stretching the Achilles tendon often is used to combat plantar fasciitis and foot pain. Massage therapy is used to therapeutically manipulate soft and connective tissue to relieve muscle spasm, tension, or stiffness. Massage can reduce pain by increasing endorphins (thereby altering the pain threshold), relieving muscle spasm, increasing circulation, increasing range of motion, and reducing local swelling and edema by increasing venous and lymphatic drainage.

Therapeutic exercise is an integral component of physical therapy, and often is an essential component of the treatment of chronic pain. Patients with chronic pain often have extended periods of decreased activity, which leads to deconditioning and can exacerbate the chronic pain condition and result in further reductions in functional capacity. Local effects of exercise include muscle strengthening, improved flexibility, increased endurance, and restoration of normal patterns of motion. Systemically, exercise strengthens muscles, builds endurance and
speed, mobilizes stiff joints, and has a wide range of cardiovascular and psychological benefits. Exercise also can promote weight loss, which can benefit a variety of chronic pain conditions including low back pain and osteoarthritis.

**Complementary and Alternative Medicine Approaches**

CAM generally is used as an umbrella term to encompass a range of therapies not typically taught in conventional medical and allied health care schools. Among these therapies are acupuncture, chiropractic, herbal medicine and dietary supplements, homeopathy, reflexology, meditation techniques, and a wide variety of other approaches. In general, CAM is used in conjunction with standard allopathic medicine rather than in lieu of it. However, in some instances, patients use alternative methods exclusively. The term “integrative medicine” is becoming increasingly used to reflect practices in which conventional and alternative treatment approaches are used.

CAM therapies are widely used by patients in the United States, who spend between $36 billion and $47 billion on such treatments each year. In a recent survey of more than 31,000 individuals, 18.9% reported the use of natural products, 11.6% reported use of deep-breathing exercises, 7.5% reported the use of chiropractic care, and 5.0% reported the use of massage. Painful conditions were prominent in the top 10 list of diseases and conditions for which CAM was used. The most common disease or condition listed was back pain; neck pain was third; joint pain was fourth; arthritis, gout, lupus, or fibromyalgia was sixth; and recurring pain was ninth.

Some CAM therapies, including chiropractic and acupuncture, are widely used in pain management and are generally acknowledged to be acceptable components of pain management programs. Others have less supporting evidence.

**Chiropractic**

Chiropractic manipulation involves the application of high-speed, low-amplitude thrusts to joints, including the spine. The alignment of the spine is said to influence the body’s nervous system and natural defense mechanisms, affecting painful conditions and overall health. Chiropractic maneuvers are used to correct the alignment of the spine. Chiropractic often is used for treating back pain, headaches, nerve inflammation, muscle spasms, and injuries, and is purported to work for a wide variety of nonmusculoskeletal ailments. The use of chiropractic manipulation for acute low back pain has the most supporting data.

There are dozens of studies investigating the use of chiropractic for treating low back pain, but many of these studies have poor methodological quality. However, one analysis of reviews of chiropractic care for low back pain found that those studies with higher methodological quality were more likely to report favorable results for chiropractic.

Patients often have a favorable perception of the chiropractic care they receive and are likely to be satisfied with such care. In one study, the outcomes of 1,633 patients with acute low back pain who presented to chiropractors, orthopedic surgeons, and primary care providers in urban and rural settings were compared. All groups had similar times to functional recovery, return to work, and complete recovery. However, patients who were treated by chiropractors reported significantly greater satisfaction with their treatment than the patients who had visited the other types of providers.

Adverse events associated with chiropractic manipulations for acute low back pain (e.g., development of cauda equina syndrome) are exceedingly rare, on the order of less than one per million treatments. In sum, the available evidence supports the use of chiropractic for treating acute low back pain, and patients may be encouraged to pursue this form of treatment if it appeals to them.

**Acupuncture**

Acupuncture has been performed for thousands of years. While there are different schools of acupuncture practice, they all center on the belief that there is a life force (called “Qi” or “chi”) that circulates through the body’s “meridians” and nourishes and protects the body. If Qi becomes imbalanced, pain and disease can result. Acupuncture is said to rebalance Qi, resulting in treatment of pain and disease. Acupuncture involves placing needles at specific acupuncture points that lie along the meridians. Needles are then stimulated manually, electrically, or with heat. Needles are left in place for 10 to 40 minutes.

There are several proposed biologically based mechanisms of action for acupuncture. Some evidence suggests that acupuncture stimulates descending pain modulation systems, while other data indicate acupuncture stimulates endorphin release.

Although acupuncture is widely used for numerous conditions, definitive evidence supporting its efficacy is lacking. Some studies have found that acupuncture is more effective at providing analgesia than sham acupuncture, but others have not. A comprehensive review conducted by the National Institutes of Health of all studies published between 1970 and 1997 concluded that, while many studies demonstrated promising data, overall results were equivocal. This review concluded that acupuncture may be a useful adjunct that may be included in a comprehensive management program. More recent data and analyses have done little to further this conclusion. Ongoing studies at the National Center for Complementary and Alternative Medicine may eventually provide more definitive answers.

Acupuncture appears to be extremely safe, and the risk of infection is minimal when single-use needles are used. Acupuncture should be avoided in patients with severe bleeding disorders, and electrical stimulation should be avoided in patients with pacemakers.

**Herbals and Dietary Supplements**

A number of herbal and dietary supplements also have been used to manage pain and to treat underlying conditions. A reasonable amount of data supports some of these treatments (opioids themselves are derived from poppy plants). Dietary supplements also may have a potential for harm, particularly when used by patients with concomitant disease states. Herbal products carry the potential for significant herbal-drug interactions with other products that the patient may be taking. For example, St. John’s wort, which a patient may be using to treat comorbid depression, interacts with dozens of prescription medications. Other products, such as kava, which a patient might be using to manage anxiety, may increase risk for hepatotoxicity. While a fair body of research exists for some products, many herbal and dietary supplements do not have well-defined safety and efficacy profiles. Patients should be reminded that just because a product is “natural” does not mean that it is safe. (A good example to use is poison ivy—it is a natural plant, but obviously something that patients want to avoid.)

The Dietary Supplement and Health Education Act (DSHEA) of 1994 gives the Food and Drug Administration (FDA) limited regulatory authority over dietary supplements. DSHEA allows dietary supplements to be sold without having to go through an
FDA approval process for efficacy and safety, and greatly expanded the marketing of these products in the United States. Under DSHEA, manufacturers are responsible for ensuring that their products are safe and contain the listed ingredients. In addition, quality control processes used to manufacture dietary supplements are not strictly regulated; therefore, contamination and adulteration are more likely to occur. There is also the potential that dietary-supplement products will not contain the amounts of ingredients listed on their product labels.

Several privately run organizations have developed programs to address manufacturing practices for dietary supplements, including the U.S. Pharmacopeia (USP) Dietary Supplement Verification Program, the ConsumerLab.com program, and the NSF International certification program. Products that are approved by one of these programs may provide greater assurance to patients that they contain the appropriate ingredients and are not contaminated.

Of products used in the treatment of pain, the dietary supplements chondroitin and glucosamine have the greatest supporting evidence and have become popular among patients for treating osteoarthritis. Clinical trials show glucosamine to be effective for reducing osteoarthritis pain, but data supporting chondroitin are equivocal. Glucosamine is the first substance shown to repair or reverse changes in osteoartotic cartilage, and the American Pain Society currently recommends that adults with osteoarthritis use 1,500 mg of oral glucosamine daily.56–58

There are literally thousands of products that are used by patients with pain, each with its own unique efficacy, safety, and drug interaction profile. A sampling of dietary supplements used in pain management for which at least some studies have demonstrated efficacy are shown in Table 7.59,60 Patients should be questioned about their use of herbal and dietary supplement products during regular assessments and reassessments. Products that are used and their perceived effects should be documented. Pharmacists also should consider obtaining access to a comprehensive reference (such as one of those listed in the Appendix), and consult these resources to ensure that there are no serious safety concerns about the product or potential interactions with the patient’s medications or disease states.

Other CAM Therapies

Other nontraditional approaches used in the treatment of pain include magnets, feng shui, crystals, and homeopathy. Many of these interventions have few, if any, data to support their use. Nonetheless, many carry a strong emotional appeal for patients. Patients who feel alienated from the mainstream health care system may be particularly drawn to alternative health care approaches.

Although data may be lacking to support many CAM therapies, a number of patients believe that they derive benefits from them. This may result in part because many CAM providers advocate patient self-efficacy (i.e., the patient’s confidence in his or her ability to manage disease and interact with the health care system), which can independently benefit patients.

Telling patients that treatments they believe in are not truly helpful can be counterproductive to establishing a good patient-provider relationship. While the cost of CAM therapies can be an issue, many CAM approaches, particularly those designed to affect the flow of energy (such as wearing crystals or strategically placing objects throughout one’s home), are generally safe. Therefore, if the patient ascribes a benefit to the treatment, it is best to support the patient’s decision unless it appears that the patient is being harmed. On the other hand, patients who seek guidance about such therapies should be advised that, generally speaking, there is little evidence to support their use and should be educated about the substantial body of evidence describing the risks and benefits of traditional medical approaches.

**Pharmacologic Treatment Options for Pain**

Numerous pharmacologic agents are used in the management of pain. Selection among available treatment options can be made following general guiding principles about the nature and severity of the pain.

The World Health Organization (WHO) has developed guidelines for the treatment of cancer pain referred to as the “analgesic ladder” (Figure 3).61 This ladder provides a general guideline for medication selection for pain of varying intensities. Mild pain usually is treated with a nonopioid analgesic and/or an adjuvant. As pain intensifies, opioids can be added to the treatment regimen. If pain is persistent, medication should be administered on a regular schedule (“around the clock”), with an immediate-release product available for breakthrough pain on an as-needed basis. According to WHO, this treatment protocol effectively relieves pain in 80% to 90% of patients with cancer.61 These guidelines are generally applicable to other types of pain as well.

One common misconception about the WHO treatment ladder is that patients should begin treatment on the bottom “step” of the ladder and then progress upward. This is not the case. If the patient presents with severe pain, he or she should begin treatment with medications that are appropriate for managing severe pain, which are at the top of the ladder. Mild to moderate pain is often managed with simple analgesics such as aspirin, acetaminophen, NSAIDs, or cyclooxygenase-2 (COX-2) inhibitors. Opioids remain the mainstay of therapy for moderate to severe pain, particularly when pain has a major central component. Certain pain states appear more responsive to some analgesics than others. For example, pain mediated by prostaglandins, such as menstrual pain, tends to respond well to NSAIDs, which reduce prostaglandin production, but is partially responsive to traditional analgesics. Combinations of opioids with acetaminophen and/or NSAIDs produce synergistic analgesic effects and are often used, particularly for moderate pain. Neuropathic pain is responsive to a number of adjuvant agents that are not generally used for nociceptive pain.

While treatment normally is based on the current presence of pain, preemptive analgesia sometimes is used when painful experiences are anticipated. Preemptive analgesia involves the administration of an analgesic agent prior to a painful event, such as surgery. Animal models have clearly demonstrated a benefit of preemptive analgesia by preventing peripheral and central sensation, resulting in a reduction of postsurgical pain. Results in humans appear promising as well but are less conclusive.15 Some, but not all, studies have shown a reduction in postoperative opioid consumption or development of phantom limb pain following amputation when preemptive analgesia is used.15

**Acetaminophen**

Acetaminophen has both analgesic and antipyretic properties similar to those of aspirin, but has few anti-inflammatory properties (Table 8). It is a widely used option for the management of mild to moderate pain and is particularly useful for patients who cannot tolerate aspirin or have contraindications to its use.62 It is
recommended as first-line therapy for a variety of pain states, including low back pain and osteoarthritis.\(^63,64\) Although it has been commercially available for decades, its mechanism of action is not completely understood. It is believed to act by centrally inhibiting prostaglandin synthesis and peripherally blocking the generation of pain impulses.\(^65\) There is some evidence to suggest that it acts centrally by inhibiting COX-3.\(^66\)

At recommended dosages, acetaminophen normally is well tolerated, but there are infrequent reports of dermatologic reactions (i.e., rash) at therapeutic dosages.\(^62\) Repeated use of acetaminophen at doses higher than 2 g daily for a week or more may increase the hypoprothrombinemic response to oral anticoagulants like warfarin in some patients.\(^67\) There are no other clinically relevant drug interactions with acetaminophen, making it a

Table 7. | Common Dietary Supplements Used in Pain Management

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Selected Uses in Pain Management</th>
<th>Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-adenosylmethionine (SAM-e)</td>
<td>OA, RA, fibromyalgia</td>
<td>No known serious toxicities; may interact with antidepressant drugs including monoamine oxidase inhibitors, dextromethorphan, levodopa, meperidine, pentazocine, tramadol</td>
</tr>
<tr>
<td>Devil’s claw Harpagophytum procumbens</td>
<td>OA, RA, gout, myalgia, fibrositis, lumbago, tendonitis, pleuritic chest pain, and migraine</td>
<td>Generally well tolerated; avoid use in patients with cardiovascular disease, diabetes, peptic ulcer disease</td>
</tr>
<tr>
<td>Ginger Zingiber officinale</td>
<td>OA, RA, migraine</td>
<td>Increased risk for bleeding; avoid concomitant use with anticoagulant or antiplatelet drugs</td>
</tr>
<tr>
<td>Avocado/soybean unsaponifiables</td>
<td>OA</td>
<td>One case report of reduced anticoagulation with warfarin</td>
</tr>
<tr>
<td>Cat’s claw Uncaria guianensis Uncaria tomentosa</td>
<td>RA, OA</td>
<td>Can cause HA, dizziness, and vomiting; may interact with antihypertensive drugs, cytochrome P-450 3A4 substrates, and immunosuppressants</td>
</tr>
<tr>
<td>Thunder God vine Tripterygium wilfordii</td>
<td>RA, systemic lupus erythematosus, multiple sclerosis</td>
<td>Thought to be teratogenic; may suppress immune function</td>
</tr>
<tr>
<td>Gamma linoleic acid</td>
<td>RA, painful diabetic neuropathy, mastitis, premenstrual syndrome, multiple sclerosis</td>
<td>Apparent anticoagulant effects; may interact with anticoagulants and antiplatelet drugs as well as phenothiazines</td>
</tr>
<tr>
<td>Fish oil</td>
<td>OA, RA</td>
<td>Generally well tolerated but may cause GI effects; large doses may increase bleeding risk, especially if coadministered with anticoagulant or antiplatelet drugs</td>
</tr>
<tr>
<td>Magnesium</td>
<td>HA, fibromyalgia</td>
<td>Generally safe in appropriate doses; may cause GI adverse effects; may interact with aminoglycoside, quinolone, and tetracycline antibiotics, bisphosphonates, calcium channel blockers, potassium-sparing diuretics, and skeletal muscle relaxants</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>HA (migraine)</td>
<td>No reported toxic effects; numerous drugs can affect riboflavin levels</td>
</tr>
<tr>
<td>Feverfew Tanacetum parthenium</td>
<td>HA (migraine)</td>
<td>May cause GI adverse effects; may inhibit platelet aggregation; nonsteroidal anti-inflammatory drugs may reduce the effects of feverfew</td>
</tr>
<tr>
<td>Butterbur root Petasites hybridus</td>
<td>HA</td>
<td>Patients should use only butterbur products that are certified and labeled as UPA free; UPA constituents are considered hepatotoxic, carcinogenic, mutagenic, and renally toxic</td>
</tr>
<tr>
<td>Alpha lipoic acid</td>
<td>Diabetic neuropathy</td>
<td>May produce rash; paresthesias may transiently worsen at initiation of therapy; may produce additive hypoglycemic effects when combined with insulin or oral hypoglycemic agents</td>
</tr>
</tbody>
</table>

GI = gastrointestinal; HA = headache; OA = osteoarthritis; RA = rheumatoid arthritis; UPA = unsaturated pyrrolizidine alkaloid.

Source: References 59 and 60.
useful choice for patients receiving additional medications. In addition, because it exhibits only weak inhibition of prostaglandin synthesis, it may be used by patients who experience gastrointestinal (GI) adverse effects with NSAIDs.63

Although acetaminophen is generally accepted as safe at recommend dosages, excessive use or overdose can cause elevation of hepatic enzymes, hepatic damage, fulminant hepatic failure, and death. Hepatotoxicity has been reported after single overdoses involving 7.5 g to 15 g of acetaminophen.64 Because of this risk, the maximum recommended daily dosage of acetaminophen is 4 g. Several conditions can increase the risk of acetaminophen toxicity, including hepatitis and other liver diseases (e.g., cirrhosis), chronic alcohol use or binge drinking, and fasting. Use of medications that induce cytochrome P-450 2E1 (e.g., barbiturates, phenytoin, carbamazepine, rifampin, isoniazid, phenobarbital, omeprazole) also can increase the risk.65 A few case reports have documented alcohol-acetaminophen toxicity in “social drinkers,” although in these retrospective case reports, it is difficult to determine whether the use of acetaminophen was within the therapeutic range.66,67

Hepatic toxicity related to acetaminophen overdose is the cause of about 57,000 emergency department visits, 26,000 hospitalizations, and 458 deaths each year in the United States. When suicide attempts and accidental poisonings are removed from those figures, 13,000 emergency department visits, 2,200 hospitalizations, and 100 deaths remain and are presumed to result from unintentional overdoses. However, calls to poison control centers and spontaneous reports to the FDA suggest that these numbers may underestimate the scope of the problem.68

There is some evidence that regular use of acetaminophen (as well as other analgesics) may result in chronic renal failure, but available data are conflicting. In a study of 926 patients with early-stage renal disease and 998 controls, regular use of either acetaminophen or aspirin was associated with a 2.5-fold relative risk of chronic renal failure from any cause.69 However, an analysis of data from enrollees in the Physician’s Health Study did not find such an association.70 A study of the women in the Nurses’ Health Study found that higher lifetime use of acetaminophen was associated with an increased risk for reduced renal function, but aspirin and NSAIDs were not.71

**Nonsteroidal Anti-Inflammatory Drugs**

The NSAIDs have analgesic, antipyretic, and anti-inflammatory actions. They comprise a broad category of drugs, with more than 20 different compounds on the market, and are the most commonly prescribed analgesics in the United States (Table 8).72,73 They are particularly useful for treating mild to moderate pain mediated by prostaglandins, such as postsurgical pain, rheumatoid arthritis, osteoarthritis, and menstrual pain.74,75

These agents produce analgesia by inhibiting COX-1 and COX-2 enzymes, which decreases the production of prostaglandins from arachidonic acid. While prostaglandins do not produce pain directly, they lower the threshold for pain transduction by sensitizing nociceptors to bradykinin and histamine. Therefore, preventing the production of prostaglandins reduces the sensitivity of nociceptors and raises the pain threshold. NSAIDs are less effective for pain states that have little prostaglandin activity such as pressure from edema or neuropathic pain.76,77

Although inhibiting the production of prostaglandins is an effective method of producing analgesia, it also is associated with several class-specific adverse events, including GI adverse events, renal adverse events, and effects on platelet activity (Table 9). Aspirin and indomethacin, the most potent inhibitors of COX-1, are the two NSAIDs associated with the most GI adverse events.78,79

**Salicylates**

Aspirin (acetylsalicylic acid) is the most widely used salicylate. Aspirin is an anti-inflammatory agent and effective analgesic for managing mild to moderate pain. Aspirin primarily acts in the periphery, although some evidence suggests that aspirin also provides analgesia through a central mechanism.

As with the other NSAIDs, gastric irritation is a common adverse effect of aspirin therapy. The majority of patients develop acute erosions and petechiae following ingestion of 300 mg or
Table 8. | Selected Nonopioid Analgesics

<table>
<thead>
<tr>
<th>Medication (Brand Name)</th>
<th>Average Adult Dose (mg)</th>
<th>Dosing Frequency (hr)</th>
<th>Maximum Daily Dosage (mg)</th>
<th>Dosing Forms</th>
<th>Adverse Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (Tylenol®, numerous others)</td>
<td>500–1,000</td>
<td>4–6</td>
<td>4,000</td>
<td>Multiple oral forms, rectal suppositories</td>
<td>Hepatic toxicity with overdosage; high dosages may increase international normalized ratio in patients taking warfarin</td>
<td>Does not have anti-inflammatory effects of NSAIDs; useful in patients intolerant to NSAIDs</td>
</tr>
<tr>
<td><strong>SALICYLATES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (numerous)</td>
<td>500–1,000</td>
<td>4–6</td>
<td>4,000</td>
<td>Multiple oral forms, rectal suppositories</td>
<td>NSAID class effects</td>
<td>Should not be used in children under age 12 yr with possible viral illness due to risk of Reye’s syndrome; antiplatelet effects</td>
</tr>
<tr>
<td>Choline magnesium trisalicylate (Trilisate®, Tricosal®)</td>
<td>1,000–1,500</td>
<td>12</td>
<td>2,000–3,000</td>
<td>Multiple oral forms, rectal suppositories</td>
<td>NSAID class effects</td>
<td>Does not increase bleeding time</td>
</tr>
<tr>
<td>Diflunisal (Dolobid®)</td>
<td>1,000 initial, 500 subsequent</td>
<td>8–12</td>
<td>1,500</td>
<td>Multiple oral forms</td>
<td>NSAID class effects; hypersensitivity can cause life-threatening reaction</td>
<td>Less GI irritation and fewer platelet effects than aspirin</td>
</tr>
<tr>
<td><strong>PROPIONIC ACID DERIVATIVES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (Advil®, Motrin®, Nuprin®, others)</td>
<td>200–400</td>
<td>4–6</td>
<td>2,400</td>
<td>Multiple oral forms, rectal suppositories</td>
<td>NSAID class effects</td>
<td>Fewer GI effects than other OTC NSAIDs</td>
</tr>
<tr>
<td>Ketoprofen (Orudis®, Actron®)</td>
<td>OTC</td>
<td>12.5–25 50–75</td>
<td>4–6 6–8</td>
<td>75 300</td>
<td>Tablets Capsules</td>
<td>NSAID class effects; extended-release capsules not recommended for acute pain</td>
</tr>
<tr>
<td>Naproxen (Naprosyn®, Naprelan®)</td>
<td>500 initial, 250 subsequent</td>
<td>6–8</td>
<td>1,500</td>
<td>Multiple oral forms</td>
<td>NSAID class effects, pseudoporphyria</td>
<td>OTC forms available</td>
</tr>
<tr>
<td>Oxaprozin (Daypro®)</td>
<td>600</td>
<td>12–24</td>
<td>1,200</td>
<td>Caplets</td>
<td>NSAID class effects, photosensitivity, rash</td>
<td>Long half-life (24–69 hr)</td>
</tr>
<tr>
<td><strong>ACETIC ACID DERIVATIVES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac (Voltaren®, Arthrotec®)</td>
<td>25–100</td>
<td>8–24 (depending on formulation)</td>
<td>200</td>
<td>Multiple oral forms, gel, ophthalmic solution</td>
<td>NSAID class effects</td>
<td>Once-daily formulation available; Arthrotec is diclofenac combined with misoprostol and is in pregnancy category X</td>
</tr>
<tr>
<td>Etodolac (Lodine®)</td>
<td>200–400</td>
<td>6–8</td>
<td>1,000–1,200</td>
<td>Multiple oral forms</td>
<td>NSAID class effects</td>
<td>Extended-release product available</td>
</tr>
<tr>
<td>Indomethacin (Indocin®, Indochron ER®)</td>
<td>25</td>
<td>8–12</td>
<td>200</td>
<td>Multiple oral forms, rectal suppositories</td>
<td>NSAID class effects, ocular effects (corneal deposits, retinal disturbances); exacerbation of Parkinson’s disease, epilepsy, or psychiatric disorders</td>
<td>Use limited due to adverse events</td>
</tr>
</tbody>
</table>

Continued on next page
600 mg of aspirin. While most ulcerations heal without significant harm, occasionally bleeding ulcers or perforations develop and require hospitalization for treatment. Enteric-coated forms of aspirin have been shown to reduce mucosal lesions and local gastric irritation but do not appear to reduce the risk of major upper GI bleeding. Endoscopic evaluation has shown that buffered and nonbuffered forms of aspirin produce similar degrees of mucosal damage. Studies evaluating the use of aspirin for cardioprotection have not found that lower doses reduce the risk for major GI bleeding.

The risk of GI irritation is increased when aspirin is coadministered with other NSAIDs. Aspirin is contraindicated in patients with bleeding disorders and should not be used to treat chicken pox or influenza in patients under 12 years of age because of the risk of Reye's syndrome. Aspirin must be used with caution in patients with impaired renal function, erosive gastritis, peptic ulcer disease, and gout. High-dose aspirin, which sometimes is used to treat inflammatory arthritis, may cause tinnitus or other auditory alterations.

Some patients are hypersensitive to aspirin. Such patients may experience either a respiratory reaction (rhinitis, asthma, nasal polyps) or a systemic reaction (urticaria, wheals, angioneurotic edema, hypotension, shock, syncope). This condition may occur in up to 25% of middle-aged patients with asthma, nasal polyps, or chronic urticaria. Patients who have aspirin hypersensitivity are more likely to develop hypersensitivity to other NSAIDs as well.

Because of the risks associated with aspirin use, newer NSAIDs have largely replaced its use as an analgesic, anti-inflammatory, and antipyretic agent. Low-dose aspirin remains widely used for the primary and secondary prevention of cardiovascular events.

Nonacetylated salicylates (choline magnesium salicylate and sodium salicylate) were developed to reduce the risks for GI

<table>
<thead>
<tr>
<th>Table 8.</th>
<th>Selected Nonopioid Analgesics (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication (Brand Name)</td>
<td>Average Adult Dose (mg)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>FENAMATES</td>
<td></td>
</tr>
<tr>
<td>Meclofenamate (Meclomen®)</td>
<td>50–100</td>
</tr>
<tr>
<td>Mefenamic acid (Ponstel®)</td>
<td>500 initial dose, then 250</td>
</tr>
<tr>
<td>ENOLIC ACIDS/BENZOTHIAZINE DERIVATIVES</td>
<td></td>
</tr>
<tr>
<td>Meloxicam (Mobic®)</td>
<td>7.5–15</td>
</tr>
<tr>
<td>Piroxicam (Feldene®)</td>
<td>20–40</td>
</tr>
<tr>
<td>PYRROLEACETIC ACIDS</td>
<td></td>
</tr>
<tr>
<td>Ketorolac (Toradol®)</td>
<td>30 or 60 IM or 30 IV initially, 15 or 30 IV or IM subsequently</td>
</tr>
<tr>
<td>Tolmetin (Tollectin®)</td>
<td>200–600</td>
</tr>
<tr>
<td>COXIBS</td>
<td></td>
</tr>
<tr>
<td>Celecoxib (Celebrex®)</td>
<td>200–400</td>
</tr>
<tr>
<td>Valdecoxib (Bextra®)</td>
<td>10–20</td>
</tr>
</tbody>
</table>

^Sustained-release preparations available.
^1250 on first day.

GI = gastrointestinal; IM = intramuscular; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter; URI = upper respiratory infection.

Source: References 15 and 43.
adverse events and platelet inhibition associated with aspirin, while retaining the analgesic and anti-inflammatory effects. These drugs can be tolerated by patients who are allergic to aspirin. Although the risk is less than that with aspirin, these agents still are associated with gastric injury, and they are not more effective than aspirin. Diflunisal, a derivative of salicylic acid, does inhibit prostaglandin synthesis and provides analgesic and anti-inflammatory effects similar to those seen with 2 g to 4 g of aspirin daily, with fewer GI adverse events. However, platelet inhibition does occur and can cause serious GI bleeding.

Other Nonselective NSAIDs

Nonselective NSAIDs can be classified by their chemical structure, but it does not appear that any class has a therapeutic advantage over the others. Individual responses to different NSAIDs vary, and it is difficult to predict which will produce the greatest response in a given patient. Therefore, failure to achieve an adequate response with one NSAID does not preclude a trial with another agent. Several trials of 2 to 3 weeks with different agents may be appropriate.

Serious, potentially fatal GI adverse events, including perforation, ulceration, and bleeding, have been reported with NSAID use. Clinical upper-GI adverse events affect 2% to 4% of patients using NSAIDs. The risk for hospitalization for a serious GI adverse event with NSAIDs is 1% to 2%. However, the risk increases with advancing age. The risk of GI bleeding associated with NSAID use in patients 60 years of age or older is 3% to 4%. The risk is approximately 9% in patients at least 60 years of age with a history of GI bleeding.

One estimate found that among arthritis patients alone, approximately 107,000 patients are hospitalized for NSAID-related GI complications and at least 16,500 patients die from prescription and nonprescription NSAID-related bleeding annually in the United States.

The prostaglandin analog misoprostol, proton pump inhibitors, and double doses of H₂-receptor antagonists have been shown to reduce the risk for NSAID-associated gastric and duodenal ulcers, and misoprostol has been shown to reduce the risk of perforation hemorrhage. However, diarrhea commonly occurs with misoprostol; proton pump inhibitors and H₂-receptor antagonists are better tolerated. The risk for GI bleeding also is reduced with lower dosages of NSAIDs.

Several drug interactions have been reported with the use of NSAIDs. Plasma concentrations of digoxin are increased during

### Table 9. | Class Effects of Nonselective NSAIDs

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Situations That Place Patients at Increased Risk</th>
<th>Management Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal effects including dyspepsia, peptic ulcer, perforation, bleeding</td>
<td>Elderly History of peptic ulcer disease Concomitant treatment with corticosteroids or anticoagulants High dosages</td>
<td>Select NSAIDs with lower risk Use low doses Administer with food Avoid alcohol Use gastroprotective agents</td>
</tr>
<tr>
<td>Hepatic dysfunction and necrosis</td>
<td>Alcoholism History of current or past hepatic disease Elevated hepatic enzymes</td>
<td>Monitor hepatic enzymes</td>
</tr>
<tr>
<td>Bleeding due to inhibition of platelet aggregation / prolonged prothrombin times</td>
<td>Use of anticoagulants Thrombocytopenia Surgery Some forms of cancer</td>
<td>For patients at high risk, use acetaminophen or select NSAIDs with decreased bleeding risk; discontinue NSAID use 2-3 days prior to surgery</td>
</tr>
<tr>
<td>Renal insufficiency or failure</td>
<td>Elderly Hypovolemic History of renal disease Use of medications that reduce renal perfusion (e.g., diuretics) Other diseases that affect renal function (e.g., hypertension, congestive heart failure, diabetes)</td>
<td>Use low doses Monitor renal function Avoid indomethacin</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>Patients who have experienced hypersensitivity to one NSAID may have cross-sensitivity</td>
<td>Monitor for signs of respiratory reactions or urticaria/angioedema</td>
</tr>
<tr>
<td>CNS dysfunction—attention or memory deficits, headache, tinnitus</td>
<td>Elderly Use of other medications that affect CNS function</td>
<td>Use low doses Switch to another NSAID or drug class</td>
</tr>
</tbody>
</table>

*This property of certain NSAIDs, aspirin in particular, is used for cardioprotection in selected patients.

CNS = central nervous system; NSAID = nonsteroidal anti-inflammatory drug.

Source: Reference 15.
coadministration with ibuprofen, and ibuprofen may be associated with worsening condition in patients with congestive heart failure.\textsuperscript{68} The NSAIDs reduce the efficacy of antihypertensive medications, increasing the risk of stroke, end-stage renal disease, and congestive heart failure.\textsuperscript{68,94,95} Therapy with NSAIDs generally should be avoided in patients who are taking warfarin, which has antiprothrombin effects and increases the prothrombin time, thus augmenting the risk for bleeding.\textsuperscript{24} Alcohol should be avoided in patients taking NSAIDs, as it can cause dizziness and drowsiness, and impair the ability to perform tasks that require mental alertness.\textsuperscript{65}

Regular use of NSAIDs has been shown to reduce the cardioprotective effects of aspirin. In a subgroup analysis of the Physician’s Health Study, aspirin provided a 44% reduction in risk of a first myocardial infarction (MI). In these individuals, the use of NSAIDs on at least 60 days per year was associated with a 2.9-fold increased risk for MI compared with no use of NSAIDs. Less frequent use of NSAIDs was not associated with an increased risk.\textsuperscript{93} Aspirin reduces the risk for MI by irreversibly blocking the COX-1 enzyme. Nonselective NSAIDs also block COX-1, but the effect is reversible. Dosing of nonselective NSAIDs prior to aspirin leads to competitive inhibition for aspirin binding to COX-1, thereby reducing the cardioprotective effects of aspirin.\textsuperscript{96} Administration of aspirin prior to the NSAID seems to circumvent the competitive inhibition and retains the cardiovascular benefits of aspirin.\textsuperscript{96}

Renal effects of NSAIDs include changes in sodium excretion, tubular function, filtration rate, and renal plasma flow. Acute renal failure has been reported in some patients.\textsuperscript{79} Certain patients are at increased risk for renal toxicities, including patients older than age 65 years and those with hypertension, heart failure, or preexisting kidney or liver disease. In general, NSAIDs should not be used by patients with chronic renal insufficiency.\textsuperscript{28} Caution must be exercised in treating patients with decreased cardiac output, because NSAIDs cause sodium and fluid retention.\textsuperscript{75}

**Cyclooxygenase-2 Selective Inhibitors**

The anti-inflammatory properties of NSAIDs result from COX-2 inhibition, while GI and renal toxicities result from COX-1 inhibition. Therefore, agents that selectively inhibit COX-2, known as coxibs, have been developed in an effort to create analgesics with improved GI and renal tolerability. Currently available agents include celecoxib and valdecoxib; a third coxib, rofecoxib, was widely used before it was removed from the global market in September 2004 due to concerns about cardiovascular safety. Other coxibs include lumiracoxib, which is approved for use in the United Kingdom, and etoricoxib, which has been approved for use in Europe. Both remain investigational in the United States. An injectable coxib, parecoxib, also is under investigation. The efficacy profiles of coxibs are similar to those of the traditional NSAIDs, but they are associated with lower instances of GI adverse events, including ulcers and bleeding complications.\textsuperscript{56,86} Coxibs have been associated with acute renal failure at recommended dosages, but the risk seems to be reduced compared with nonselective agents.\textsuperscript{98,99}

While the incidence of GI adverse events appears to be reduced with coxibs, concerns about their cardiovascular safety have been increasing, and led to the market withdrawal of rofecoxib. Agents that inhibit COX-1 also have antithrombotic properties (i.e., inhibition of platelet aggregation), whereas the coxibs lack these properties.

Several large, randomized trials have produced data regarding the risk of cardiovascular events with coxibs. The Vioxx Gastrointestinal Outcomes Research Study (VIGOR; 8,076 patients) found that the rates of cardiovascular adverse events were increased in patients receiving rofecoxib compared with naproxen (the NSAID comparator).\textsuperscript{100} The study authors concluded that it was unclear whether the increase in cardiovascular events in VIGOR represented an adverse effect of rofecoxib or a protective effect of naproxen (which has antiplatelet effects).

The Celecoxib Long-term Arthritis Safety Study (CLASS; 8,059 patients) found no significant difference between celecoxib and the NSAID comparators; however patients in this trial were allowed to receive aspirin, which may have complicated the results.\textsuperscript{96,100,101} The event rates in CLASS and VIGOR were compared with event rates in 23,407 patients receiving placebo in a meta-analysis.\textsuperscript{100} This comparison revealed a significant increase in the rate of MI with both COX-2 inhibitors.\textsuperscript{100}

An analysis of the clinical trial database of nearly 8,000 patients with rheumatoid arthritis or osteoarthritis treated with valdecoxib found no increase in the rates of adverse cardiovascular events. Similarly, no increase in adverse events was seen in patients receiving valdecoxib following general surgery. However, two studies have found an increased risk of cardiovascular adverse events in patients undergoing coronary artery bypass graft surgery.\textsuperscript{102,103}

An epidemiologic study analyzed the medical records of 1.4 million patients insured by Kaiser Permanente who were between 18 and 84 years of age and treated with a coxib or nonselective NSAID between January 1999 and December 2001. This analysis included 40,405 patients treated with celecoxib and 26,748 treated with rofecoxib. Patients taking rofecoxib had significantly higher rates of adverse cardiac events than patients taking celecoxib.\textsuperscript{104} There were 8,199 acute cardiac events within the study cohort (6,675 acute MI; 1,524 sudden cardiac death). The use of rofecoxib at dosages of at least 25 mg daily produced a 3.15-fold increased risk of an acute cardiac event. Naproxen use also significantly increased cardiovascular risk, as did “other NSAIDs,” indomethacin, and possibly diclofenac.\textsuperscript{104} The risk was increased in patients taking lower-dose rofecoxib compared with celecoxib.\textsuperscript{104}

Despite the concerns about the cardiovascular safety of rofecoxib that were raised by these trials, data were considered inconclusive until the results of a prospective, randomized trial were released in September 2004. In the Adenomatous Polyp Prevention of Vioxx (APPROVe) trial, which was designed to assess whether rofecoxib prevented benign sporadic colonic adenomas, safety monitoring found that patients taking rofecoxib had a significantly increased risk of MI and thrombotic stroke compared with patients taking placebo.\textsuperscript{105} Based on these findings, the study was prematurely halted and rofecoxib was withdrawn from the market.

It remains unclear whether the increased cardiovascular risk seen with rofecoxib was drug specific or applies to other COX-2 coxibs. A proposed mechanism for the increased risk is that coxibs reduce prostaglandin I\textsubscript{2} formation, resulting in elevated blood pressure, accelerated atherogenesis, and increased thrombotic response to a ruptured plaque.\textsuperscript{105} Although the increased cardiovascular risk has not been documented across the coxib class, this proposed mechanism would theoretically apply to the other agents. Additional research is needed to further ascertain whether this is a class effect.

**Opioids**

Opioids are naturally occurring, semisynthetic, or synthetic compounds that bind to opiate receptors, mimicking endoge-
nous endorphins by stimulating inhibitory descending pathways in the CNS, resulting in analgesia. Opioids are the agents of choice in the management of severe acute pain and moderate to severe pain associated with cancer. In addition, their use in the management of moderate to severe chronic nonmalignant pain and severe neuropathic pain has gained acceptance in recent years.

Opioids exert their analgesic effects by activating opioid receptors in the CNS. The interaction of exogenous opioids with these receptors is similar to the interaction produced by the endogenous endorphins. They also appear to have some analgesic effects in the periphery. There are three generally recognized classes of opioid receptors—mu, delta, and kappa. Sigma and epsilon receptors also have been identified, but they are not opioid specific and their activation does not result in analgesia. Differences in binding affinity to opioid receptors account for the variable physiologic effects among opioids. Opioids are classified by receptor interactions (agonist, partial agonist, agonist-antagonist, and antagonist), the pain intensity for which they are conventionally used (moderate or severe), and their duration of action (i.e., immediate-release opioids, long-acting opioids such as methadone and buprenorphine, and immediate-release opioids in controlled-release delivery systems).

Pure agonists (e.g., morphine) bind with mu receptors and produce an analgesic effect that increases with dose without a ceiling effect. (However, combination products of pure opioids and nonopioids are limited by the maximal dose of the nonopioid.) The dose of pure agonists is limited only by tolerability to the associated adverse events. These agents are most widely used for pain management. Mixed agonist-antagonists partially activate the mu receptor as an agonist and partially activate the kappa receptor as an antagonist. Partial agonists bind with relatively low affinity to opioid receptors and have reduced efficacy compared with the pure agonists. These agents also can produce withdrawal symptoms in patients who are physically dependent on pure agonists. This effect may be problematic for patients with pain who also are being treated for substance abuse with buprenorphine. Partial agonists bind with relatively low affinity to opioid receptors, have reduced efficacy compared with the pure agonists, and have a ceiling dose. Competitive inhibitors such as naloxone antagonize the effects of agonists by interfering with the binding of agonists to the opiate receptors.

Based on the WHO analgesic ladder, patients with moderate to severe pain may be appropriate for treatment with opioids. Patients with somatic or visceral pain appear to be more responsive to opioids than those with neuropathic pain. However, recent studies have found that many patients with neuropathic pain do achieve effective analgesia with opioids, including patients with painful diabetic neuropathy and postherpetic neuralgia. In many cases, an adequate trial with appropriate dose titration is necessary to achieve desired effects. However, not all pain should be managed with opioids. For example, if a patient has severe pain resulting from constipation, opioids would worsen the constipation. Resolution of the underlying condition is more likely to produce long-lasting relief.

**Opioid Selection**

Pain intensity, pharmacologic factors, coexisting conditions, and economic factors all affect the selection of opioids. For moderate pain, a combination product containing acetaminophen or an NSAID and an opioid usually is used. The dosing of such products can be increased until the maximum daily dosage of the nonopioid is reached. However, these products are all short acting and may not be optimal for patients who require opioid therapy for more than a few days. Single-agent products are more commonly used for patients with severe pain, or when around-the-clock dosing is appropriate (Table 10).

Opioid selection should be guided by the intensity and duration of pain as well as tolerance and safety considerations. Pure mu-opioid agonists are similar pharmacodynamically but have differing pharmacokinetic properties. There is considerable intravariability in the response to opioids. Thus, if a patient experiences insufficient analgesia or unacceptable adverse events with one opioid, a trial of another opioid may be appropriate.

**Pharmacokinetic Considerations**

Opioids are primarily metabolized in the liver through dealkylation, conjugation, hydrolysis, and oxidation, and primarily undergo renal excretion. Hepatic impairment can decrease metabolism of most opioids and increase their half-lives, necessitating a reduction in dosage. This effect is most pertinent for methadone, meperidine, pentazocine, and propoxyphene. Clearance of meperidine, propoxyphene, and morphine and their metabolites also is decreased by renal impairment. If renal or hepatic impairment is present, these drugs should be titrated carefully and patients should be closely monitored. Some opioids, such as morphine, meperidine, and propoxyphene, have clinically important metabolites that need to be considered during treatment. Some opioid preparations contain sulfites, which can cause allergic reactions in sulfa-sensitive patients. Other opioids are available in specialized delivery systems that affect their pharmacokinetics.

Morphine is primarily metabolized to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G can produce hyperalgesia, allodynia, and hyperactivity and appears to antagonize the analgesia provided by morphine. On the other hand, M6G has greater analgesic potency than morphine and produces fewer adverse events. Elevated concentrations of M3G, or an increased ratio of M3G to M6G, can produce allodynia, hyperalgesia, and myoclonus (sudden, involuntary jerking of a muscle or group of muscles) in a dose-related manner. If these effects occur, switching to another opioid may be warranted.

Although it is a potent analgesic, meperidine is not considered a first-line agent because of a high potential for adverse events, and it has been removed from many hospital formularies. Normeperidine, one of the metabolites of meperidine, can produce CNS excitation, with tremors, myoclonus, delirium, and seizures. Naloxone does not reverse the excitatory effects and may actually worsen them. The risk of these adverse events increases with repeated dosing and in patients with renal insufficiency. In addition, patients develop tolerance to the analgesic effects of meperidine more quickly than they develop tolerance to the CNS excitatory effects. Therefore, escalating dosages to manage pain can increase the risk of CNS adverse events. Meperidine should not be used for more than 1 or 2 days, and should be avoided in patient-controlled analgesia devices, in elderly patients, and in patients with renal impairment.

Propoxyphene also has an increased risk for inducing seizures compared with other opioids. This drawback, combined with the fact that it has not been proven to be more effective than acetaminophen, aspirin, or codeine, limits its use. In addition, propoxyphene can cause cardiac conduction abnormalities. Both propoxyphene and its metabolite norpropoxyphene contribute to the cardiotoxicity, whereas the neurotoxicity results solely from the propoxyphene. Naloxone does not reverse the cardiotoxicity associated with propoxyphene. Propoxyphene should be avoided in elderly patients.
Methadone has historically been a mainstay of treatment for opioid addiction and has recently been gaining popularity for the treatment of pain. Methadone provides analgesia via multiple synergistic mechanisms that differ in some respects from those of other opioids. Methadone is a racemic mixture; the L isomer interacts with opioid receptors, and both the L and D isomers act as NMDA receptor antagonists.\textsuperscript{115} In addition, the L isomer inhibits the reuptake of serotonin and norepinephrine.

The metabolites of methadone do not have any notable pharmacologic activity. Methadone has an elimination half-life of 30 hours, although there is significant interindividual variation. Methadone accumulates with repeated dosing, which may necessitate dosage reduction or an increase in dosing intervals for some patients. Depending on the patient, methadone may be dosed every 8, 12, 24, or 48 hours.\textsuperscript{115} Patients should be carefully reevaluated during the week following methadone initiation, and after any dosage changes. Methadone is primarily excreted by the fecal route, and renal impairment does not contribute to methadone accumulation.\textsuperscript{115}

Note that if methadone is used to treat addiction, it must be prescribed by a narcotic treatment program. However, any health care professional who can prescribe Schedule CII medications.

### Table 10. Selected Short-Acting Opioid Analgesics

<table>
<thead>
<tr>
<th>Medication (Brand Name)</th>
<th>Starting Oral Adult Dose (mg)</th>
<th>Usual Dosing Frequency (hr)\textsuperscript{a}</th>
<th>Metabolism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butorphanol (Stadol\textsuperscript{®})</td>
<td>2 (1 for nasal spray)</td>
<td>3–4</td>
<td>Extensively metabolized in the liver</td>
<td>Agonist-antagonist analgesic; has ceiling dose effect Available as a nasal spray</td>
</tr>
<tr>
<td>Codeine (many combination products)</td>
<td>15–60</td>
<td>3–6</td>
<td>Codeine is a prodrug for morphine Hepatic metabolism \textsuperscript{b} 5%–15% of the dose is eliminated as unchanged codeine and the remainder as a product of glucuronide conjugates of codeine and its metabolites</td>
<td>Use for mild to moderate pain May cause more nausea and constipation than other mu-agonist opioids ~10% of the U.S. population lacks the enzyme required to metabolize codeine to its active form and will not experience analgesia</td>
</tr>
<tr>
<td>Fentanyl (Sublimaze\textsuperscript{®}, Actiq\textsuperscript{®})</td>
<td>Transmucosal 200 µg</td>
<td>As needed, minimum of 30 minutes</td>
<td>Primarily hepatic metabolism; approximately 75% of intravenous dose excreted in urine</td>
<td>Use for severe breakthrough pain Very rapid onset of action Sustained-release transdermal patch available for severe chronic pain</td>
</tr>
<tr>
<td>Hydrocodone (many combination products available including Vicodin\textsuperscript{®}, Lorcet\textsuperscript{®}, Lortab\textsuperscript{®})</td>
<td>5–10</td>
<td>3–6</td>
<td>Metabolism includes O-demethylation (which forms hydromorphone), N-demethylation, and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxy metabolites; the O- and N-demethylation processes are mediated by cytochrome P-450 2D6 and 3A4, respectively Hydrocodone and its metabolites are eliminated primarily by the kidneys</td>
<td>Use in moderate to severe pain</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid\textsuperscript{®})</td>
<td>2–4</td>
<td>3–6</td>
<td>Metabolized primarily in the liver Excreted in the urine primarily as the glucuronidated conjugate</td>
<td>Use in severe pain</td>
</tr>
<tr>
<td>Levorphanol (Levo-Dromoran\textsuperscript{®})</td>
<td>2–3</td>
<td>6–8</td>
<td>Extensively metabolized in the liver and excreted renally as the glucuronide metabolite The glucuronide metabolite accumulates with chronic dosing</td>
<td>Use in severe pain Wait 3 days between dosage adjustments</td>
</tr>
</tbody>
</table>

Continued on next page
Fentanyl is approximately 100 times more potent than morphine but undergoes significant first-pass metabolism, reducing its efficacy when administered orally. However, it is available in two noninvasive dosage forms that deliver the drug systemically. These include a lozenge for transmucosal administration—oral transmucosal fentanyl citrate (OTFC)—and a transdermal patch system. OTFC has a rapid onset of action (within 3–5 minutes) and is widely used for the treatment of breakthrough pain. The peak effect of OTFC is 20 to 40 minutes after the start of administration. Its relatively short duration of action (2–3 hours) reduces the risk for drug accumulation with repeated dosing. Treatment with OTFC should be initiated with a 200-µg dose and then individually titrated based on patient response. Conversion guidelines based on the patient’s existing opioid usage do not exist. If the first dose is inadequate, the patient should wait 30

<table>
<thead>
<tr>
<th>Medication (Brand Name)</th>
<th>Starting Oral Adult Dose (mg)</th>
<th>Usual Dosing Frequency (hr)*</th>
<th>Metabolism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine (Demerol®)</td>
<td>50–150</td>
<td>3–4</td>
<td>Primarily hydrolyzed to meperidinic acid followed by conjugation and renal elimination; Demethylation to normeperidine is a minor metabolic pathway; Normeperidine has a longer half-life than the parent drug, can accumulate (particularly in patients with renal impairment), and is neurotoxic.</td>
<td>Use in severe pain. <strong>Do not use for more than 1–2 days</strong>. Accumulation of metabolite normeperidine causes central nervous system excitation; meperidine should be avoided in patients who have impaired renal function or who are using monoamine oxidase inhibitors. It is no longer on many hospital formularies due to the risk for adverse events. Contraindicated in patients who have received a monoamine oxidase inhibitor in the past 14 days.</td>
</tr>
<tr>
<td>Methadone (many generic forms)</td>
<td>2.5–10 (acute pain) 5–20 (chronic pain)</td>
<td>3–4 (acute) 6–8 (chronic)</td>
<td>Hepatic metabolism; majority of metabolites excreted in the liver. May accumulate with repeated dosing and require dosage reductions or longer dosing intervals (there may be up to a 20-fold interindividual variation in terminal elimination half-life and clearance).</td>
<td>Use for severe chronic pain. Some patients can be dosed every 12 hr.</td>
</tr>
<tr>
<td>Morphine (many generic forms)</td>
<td>5–30</td>
<td>3–4</td>
<td>90% of the dose is metabolized hepatically to morphine-3-glucuronide (45%–55%) and morphine-6-glucuronide (10%–15%) and other minor metabolites.</td>
<td>Use for severe pain. Morphine-3-glucuronide has neuroexcitant properties and appears to antagonize the analgesic properties of morphine.</td>
</tr>
<tr>
<td>Nalbuphine (Nubain®)</td>
<td>10</td>
<td>3–6</td>
<td>Extensive hepatic metabolism to inactive metabolites and excreted primarily in the feces.</td>
<td>Agonist-antagonist analgesic; has ceiling dose effect for analgesia and respiratory depression; often used in labor as a result of this property.</td>
</tr>
<tr>
<td>Oxycodone (Oxydose™, OxyFast®, OxylR®, Percolone®, Roxicodone™, others)</td>
<td>5–15</td>
<td>3–6</td>
<td>Extensively metabolized to noroxycodone, oxymorphine, and their glucuronides. Oxycodone and its metabolites are excreted primarily via the kidney.</td>
<td>Use for moderate to severe pain.</td>
</tr>
</tbody>
</table>

Can prescribe methadone for the treatment of pain.

Table 10. | Selected Short-Acting Opioid Analgesics (continued)
minutes from the time the first unit was started, and then use a
second unit. If pain is relieved after the second dose of 200
µg, the dosage for subsequent episodes of breakthrough pain should
be 400 µg.

The transdermal fentanyl patch provides effective analgesia over a period of 48 to 72 hours. After application, the skin under
the patch absorbs fentanyl, forming a depot of medication that is
then released systemically. Serum concentrations increase grad-
ually after the initial application, plateau between 12 and 24
hours after application, and remain relatively constant for the
remainder of the dosing interval. Patches are labeled in accordance with the average amount of drug that is delivered to the
systemic circulation per hour across average skin.

The patch should be applied to clean, dry skin on the upper
arm or torso that is free of oil, hair, scars, cuts, burns, or irritation.
The patch should be applied by pressing it into place with the
palm of the hand and applying pressure for a minimum of 30
seconds. If the patch does not stick well or becomes loose after
application, first-aid tape should be used to hold it in place. If the
patch falls off, the patient should discard it and apply a new
transdermal patch on a different skin site. Patients and their
caregivers should be instructed to avoid external sources of heat
(e.g., heating pads, sunlamps, heated water beds, electric blank-
ets, sunbathing, prolonged hot baths or showers), because these
will increase drug absorption from the patch and increase the
possibility of an overdose. The rate of fentanyl release also may
be increased in febrile or cachetic patients.

Several opioids exhibit clinically significant drug interactions
(Table 11).107 Codeine, hydrocodone, morphine, methadone, and
oxycodone are substrates of the cytochrome P-450 enzyme
CYP2D6 and may interact with agents that inhibit this isozyme.117
For example, CYP2D6 converts codeine to morphine and
hydrocodone to hydromorphone; inhibition of CYP2D6 by other
agents could result in failure of these drugs to produce adequate
analgesia.117 On the other hand, inhibition of CYP2D6 may result
in potentiation of the opioid effects of morphine, meperidine, and
methadone.117,118 Methadone also is a substrate of CYP3A4 and
can interact with other drugs that induce or inhibit this
enzyme.115 Furthermore, it can autoinduce its own metabolism at
this enzyme, increasing the rate at which it is metabolized.116 CNS
depressants, alcohol, tricyclic antidepressants (TCAs), and phen-
othiazines also may potentiate opioid effects, while phenytoin
may decrease analgesic efficacy.65 In addition, propoxyphene is an
inhibitor of CYP3A4 and can increase serum concentrations of
carbamazepine, phenobarbital, TCAs, and warfarin.65

Selection Among Routes

Table, liquid, sublingual, rectal, transdermal, transmucosal,
parenteral, and intraspinal formulations of opioids are available; the most convenient and comfortable form possible for the patient should be selected. In most cases, patients can use oral or transdermal forms of opioids. The oral route is usually preferred for treatment of chronic pain because it is convenient, flexible, and produces relatively steady blood concentrations of opioids. Transdermal fentanyl shares many of these features and has less frequent dosing (generally every 72 hours). However, it is usually more expensive than oral analgesics. Liquid oral formulations of some opioids are available for patients who have difficulty swallowing. In addition, some tablets can be crushed for administration in such patients. However, some controlled-release forms of opioids should never be crushed, because this disables the controlled-release properties of the product. Oral opioids usually take 45 minutes for onset of action, with peak effects in 1 to 2 hours. Alternate dosages routes are also appropriate for patients with dysfunction.

Intravenous (IV) administration of opioids may be appropriate for patients with acute pain because IV opioids have a more rapid onset of action. IV fentanyl has an onset of action of 1 to 5 minutes, while IV morphine has an onset of 15 to 30 minutes. Subcutaneous (SC) injections are another alternative to IV injections. In some cases, a continuous IV infusion may be used, particularly if the patient requires very large dosages. Intramuscular (IM) injections should generally be avoided because they are painful and result in wide fluctuations in absorption and peak effects. Repeated IM injections should almost never be used. IV, SC, and IM routes are generally considered to be equianalgesic. Guidelines for conversion among routes are imprecise, and switches must be closely monitored to prevent overdosing or underdosing. When switching from a parenteral route, some clinicians slowly reduce the parenteral dose while increasing the oral (or other) dose to minimize problems.

Other routes of administration are rectal and sublingual. Rectal suppositories are available for many opioids and are relatively equal to oral dosages in their potency. Sublingual opioids can provide adequate analgesia for some patients, but many opioids have poor absorption via this route. OTFC has been specifically formulated to be administered transbuccally and may be useful for treating breakthrough pain in opioid-tolerant patients. A portion of the OTFC dose is inadvertently swallowed and reaches the systemic circulation through GI absorption.

More invasive routes of administration include intraspinal (epidural and intrathecal) and patient-controlled analgesia. (The term “subarachnoid” is used interchangeably with “intrathecal.”) These routes often are used postoperatively, but they also are appropriate for a wide variety of painful conditions. Such routes may be used for patients who have not obtained adequate analgesia following trials with other regimens. There is a 10-fold difference between the potency of opioids administered epidurally and intrathecally: 10 mg of morphine IV is equivalent to 1 mg epidurally and 0.1 mg intrathecally.

### Opioid Dosing and Scheduling

A dosage of an opioid that provides sufficient analgesia for one patient may be ineffective for another patient with similar clinical characteristics, or may produce intolerable adverse effects. Guidelines for conversion among

<table>
<thead>
<tr>
<th>Opioid(s)</th>
<th>Interacting Drug(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Quinidine</td>
<td>Inhibition of conversion to morphine; decreased analgesia</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Monoamine oxidase inhibitors</td>
<td>Excitatory response (including seizures, arrhythmias, hyperpyrexia, and coma); potentially fatal interaction</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Sibutramine</td>
<td>May induce serotonin syndrome</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Selective serotonin reuptake inhibitors</td>
<td>Case reports of serotonin syndrome</td>
</tr>
<tr>
<td>Meperidine, morphine</td>
<td>Cimetidine</td>
<td>Inhibition of opioid metabolism; increased opioid effects</td>
</tr>
<tr>
<td>Methadone</td>
<td>Carbamazepine, Erythromycin, Phenytoin</td>
<td>Increased opioid metabolism; may induce withdrawal</td>
</tr>
<tr>
<td>Methadone, morphine</td>
<td>Desipramine</td>
<td>Inhibition of desipramine metabolism; toxicity possible</td>
</tr>
<tr>
<td>Controlled-release opioids</td>
<td>Metoclopramide</td>
<td>Earlier peak plasma concentration; increased sedation</td>
</tr>
<tr>
<td>Opioids (class)</td>
<td>Sedating antihistamines</td>
<td>Increased sedation</td>
</tr>
<tr>
<td>Opioids (class)</td>
<td>Butyrophenones (e.g., haloperidol)</td>
<td>Increased sedation</td>
</tr>
<tr>
<td>Opioids (class)</td>
<td>Tricyclic antidepressants</td>
<td>Increase sedation and potentiation of opioid-induced respiratory depression</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Carbamazepine</td>
<td>Increased carbamazepine levels, potential for toxicity</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Doxepin</td>
<td>Increased doxepin levels, potential for toxicity</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Metoprolol, propranolol</td>
<td>Increased plasma levels of these beta blockers</td>
</tr>
</tbody>
</table>

*Source: Reference 107.*
events. Therefore, although equianalgesic charts are available, dosage selection must always be individualized. Some patients require dosages that greatly exceed those that are on product labels. In a survey of patients with pain resulting from advanced cancer, 10% of patients required opioid dosages in excess of 2,000 mg of morphine daily, and one patient was receiving 35,000 mg of parenteral morphine every 24 hours.108,119

Patients who are “opioid naïve” (i.e., those who have had only limited prior exposure to opioids) should have treatment for severe pain initiated at a dose equivalent to 5 mg to 10 mg of morphine parenterally every 4 hours (Table 12).108 Patients who are opioid naïve are more likely to experience certain adverse effects associated with opioid therapy, such as respiratory depression. Thus, greater caution, including monitoring of respiratory function, is required when starting or increasing dosages in these patients to minimize this risk.

Dosages should be titrated at the start of therapy, and repeated dose adjustments may be necessary. If the initial dosage does not provide adequate relief, the dosage should be titrated upward until adequate analgesia is achieved or intolerable adverse events occur.

The rate of titration depends on pain severity, comorbid conditions, and the pain relief goals. Patients with moderate pain can have their dosages titrated upward by the larger of (1) the amount of the daily rescue dose or (2) 30% to 50% of the fixed scheduled dose.108 Larger dosage increases may be appropriate for more severe pain, and patients with very severe, uncontrolled pain may require rapid dose escalation until a reduction in pain is experienced. In one study, repeated IV opioid boluses, with the dosage doubled every 30 minutes until adequate analgesia was obtained, were a safe and effective strategy for managing cancer pain emergencies.120

Once an adequate dosage has been achieved, some patients with chronic pain that results from a stable disease process are able to continue to receive adequate analgesia without dosage adjustments. However, in some cases, a once-stable dose is no longer adequate. A number of factors can contribute to the loss of adequate analgesia, including true pharmacologic tolerance, disease progression, increased psychological distress, increased physical activity, initiation of another medication that interacts with the opioid, tolerance, misuse of medication, and other factors.

Although tolerance to many of the nonanalgesic effects of opioids (e.g., respiratory depression, sedation, pruritus) frequently occurs, tolerance to the analgesic effects is less common. If it does occur, increasing the dosage or switching to another opioid may improve analgesia. Some health care providers advocate the use of opioid rotation—periodically switching among opioids—in order to prevent the development of tolerance. (The term “pseudotolerance” is sometimes used to describe the situation of patients who appear to have developed tolerance as a result of other factors, such as increased activity, disease progression, or misuse of medication.)

Scheduling of dosages should be designed to optimize analgesia and patient convenience. Patients with persistent pain should receive opioids on a continuous, around-the-clock dosing schedule rather than on an as-needed basis in order to provide continuous analgesia. Short-acting opioids usually are used for the treatment of intermittent pain and as rescue doses for breakthrough pain—pain that occurs while a patient is using an around-the-clock treatment regimen. Almost all patients who receive around-the-clock treatment should have rescue doses available to use when necessary.

If patients require around-the-clock treatment for more than a few days, treatment with a controlled-release or long-acting opioid should be implemented. These agents are more convenient than those that must be dosed every 4 to 6 hours. In addition, they stabilize peaks and troughs in blood concentrations of the drug, reducing the incidence of adverse events and periods of inadequate efficacy, respectively. However, controlled-release forms should not be used to rapidly titrate doses because they require more time to achieve steady-state concentrations.108 Short-acting opioids should be used during periods of rapid titration. Once an adequate dosage is established, the treatment can be converted to a controlled-release product, with an equal amount (on a milligram basis) per 24-hour period.108

Several sustained-release products are available, including those containing fentanyl, hydromorphone, morphine, and oxycodone (Table 13).121–126 Product labeling provides recommended dosing intervals; however, individual variability in metabolism may require adjustments in administration timing for some patients. Several sustained-release morphine products are available and are administered once or twice daily. Sustained-release oxycodone is labeled for administration twice daily. Sustained-release hydromorphone was approved in September 2004 and is dosed once daily. Continuous systemic delivery of fentanyl is available from a transdermal patch that is labeled for application every 72 hours. Although some patients require methadone to be dosed every 6 to 8 hours, others require a less frequent dosing schedule. As with short-acting opioids, failure to achieve a satisfactory response with one sustained-release product does not preclude the use of another. Adequate trials of various sustained-release products should be attempted as needed in order to establish a treatment regimen that provides sufficient analgesia, is tolerable, and provides the greatest convenience for the patient.

Some sustained-release or controlled-release mechanisms for oxycodone, hydromorphone, and morphine products (i.e., OxyContin®, Palladone®, MS Contin®) are disabled by crushing the tablet. When these products are crushed and administered, the entire dosage is released at once, rather than over an extend-

<table>
<thead>
<tr>
<th>Table 12.</th>
<th>Equianalgesic Dosages of Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose Equianalgesic to 10 mg of IM Morphine (mg)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Opioid</strong></td>
<td><strong>IM</strong></td>
</tr>
<tr>
<td>Codeine</td>
<td>130</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>100</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2–3</td>
</tr>
<tr>
<td>Methadone</td>
<td>10</td>
</tr>
<tr>
<td>Meperidine</td>
<td>75</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>2</td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>100 µg/hr = 2–4 mg/hr of IV morphine</td>
</tr>
</tbody>
</table>

**IM** = intramuscular; **IV** = intravenous; **NA** = not available.

Source: Reference 108.
doses should be estimated based on equianalgesic dosing tables and then modified based on clinical response.43 Switching opioids, such as lack of efficacy, poor tolerance, a change in patient status (e.g., loss of the ability to swallow), and formulation and reimbursement issues. Thus, clinicians should be familiar with strategies for switching among opioids. The relative potency of an opioid is commonly based on a comparison to 10 mg of parenteral morphine (Table 12). Equianalgesic dosing tables may be used for guidance when switching among opioids or routes of delivery, but they do not provide absolute answers for selecting the dosage of the new opioid. A number of variables can influence the dosage selection for individual patients, including age, metabolic abnormalities, and individual idiosyncrasies. In addition, much of the available equianalgesic dosing data are derived from single-dose studies; in other cases, the data are derived from the observations of prescribers but have not been confirmed in clinical trials.30 New doses should be estimated based on equianalgesic dosing tables and then modified based on clinical response.43

If, following a reassessment of the patient, it is determined that switching opioids is indicated, the first step is to calculate the patient’s total daily opioid intake. This calculation should include both the patient’s regularly scheduled doses and the patient’s average daily dose of opioids used for breakthrough pain. Because most equianalgesic data have been determined using morphine, each opioid that the patient is taking should be converted into morphine equivalents using a standard equianalgesic table. Then, the equivalent morphine dose should be used to calculate an equivalent dosage of the new opioid.30

To account for the lack of precision of the tables and the possibility of incomplete cross-tolerance when switching among opioids, some sources recommend first dosing the new opioid at 50% to 75% of the equianalgesic dosage listed in tables.127 Patients and their caregivers should be advised that pain control may be suboptimal for a short time as the dosage is titrated. An immediate-release opioid for treating breakthrough pain should be available for rescue treatment to avoid periods of uncontrolled pain during opioid switches. A general rule of thumb for calculating the breakthrough dose is that it should be 10% to 20% of the total daily opioid dose.40 If the opioid switch is being made due to uncontrolled pain, it may not be necessary to reduce the dosage of the new opioid, and in some cases, an increase may be appropriate.66 If a more aggressive approach is used, the patient should have a reliable observer (i.e., caregiver) who can monitor for adverse events, such as excessive sedation. Following the opioid conversion, the patient should be evaluated frequently for the first 1 to 2 weeks to determine the efficacy and tolerability of the new regimen, and to assess whether the new dosage needs to be modified.

Extra caution should be used when switching patients to methadone. According to one source, published equianalgesic data for the morphine/methadone dosage ratio range from 2.5:1 to 15:1.115 Several different strategies exist for switching patients to methadone, including switching the entire dose to methadone on the first day, or gradually reducing the first opioid and increasing the methadone over 3 days. Because switching to methadone is a complex process, some authors believe it should be carried out only by health care professionals who are experienced in pain management.115

**Adverse Events**

Adverse events commonly associated with opioids include constipation, nausea and vomiting, sedation, and pruritus. Delirium may occur but is much less frequent. In addition, the risks of respiratory depression and abuse and diversion are important considerations for opioid analgesics.97 Strategies for minimizing adverse effects associated with opioids are listed in Table 14. Sedation and nausea and vomiting are common early adverse events associated with opioid therapy and usually abate within a few days of therapy. New emergence of these adverse events later in therapy suggests that the medication or its metabolites are accumulating.

Opioid receptors are located throughout the GI tract, and the binding of opioids to these receptors results in decreased peristalsis, prolonging intestinal transit time. Increased transit time allows for greater absorption of sodium and water, producing a drier stool. In addition, when the stool reaches the rectum, the effects of the opioid on the CNS may blunt sensations associated with the need to defecate. In patients receiving opioid therapy, these factors often are combined with other causes of constipation, such as reduced mobility or reduced fluid intake, which can further compound the problem. While patients often develop tolerance to other adverse effects of opioid therapy within a few days, tolerance to the constipating effects of opioids does not occur.

Because constipation is a predictable effect of opioid therapy, pharmacists should advise patients to begin using laxatives prophylactically when initiating treatment. Although first-line therapy for constipation generally involves increasing exercise, fluid intake, and dietary fiber, these interventions are usually not effective for preventing or treating opioid-induced constipation, and pharmacologic management is indicated.

Because opioids affect both peristalsis and the fluid content of the stool, treatment and prophylaxis should target these mechanisms. Stimulant laxatives are commonly used to promote...
motility; the agents of choice are senna and bisacodyl. A stool softener can be used to counteract the drying and hardening effects of increased transit time; docusate is the most widely used. However, docusate should be used only in combination with an agent that promotes motility and in patients with adequate fluid intake.

Bulking agents are not generally effective for treating opioid-induced constipation and can actually contribute to the development of fecal impaction. Fiber-based laxatives will increase the mass of the stool without increasing motility and they can be particularly dangerous for patients who have difficulty maintaining adequate fluid intake.

If constipation does develop during opioid therapy, the prophylactic regimen should be reviewed, and adjunctive agents or increased dosages of laxatives may be necessary. Other options for therapy include osmotic laxatives (mannitol, lactulose, polyethylene glycol, and sorbitol), saline cathartics (magnesium hydroxide and magnesium sulfate), suppositories, and enemas; and opioid antagonists (naloxone and nalmefone) are sometimes used with caution.

Pharmacists should also be on the lookout for symptoms that suggest the development of fecal impaction. Although some patients with fecal impaction have symptoms similar to those of constipation, others may not have GI symptoms. Instead, they may exhibit cardiovascular or respiratory problems. Other symptoms can include oozing or explosive diarrhea (as stool moves around the impaction), leaking stool when coughing, nausea, vomiting, abdominal pain, and dehydration. If fecal impaction is not recognized and treated, it can be life threatening.

Respiratory depression is perhaps the most serious potential adverse event associated with opioid therapy. Opioids depress all phases of respiratory activity, including rate, minute volume, and tidal exchange; and indiscriminate dosing can lead to serious, and potentially fatal, respiratory depression. This risk is reduced in patients with more severe pain. Clinical experience and experimental studies have found that pain antagonizes the respiratory-depressant effects of opioids. Therefore, the more pain a patient experiences, the less likely he or she is to experience adverse respiratory effects of opioids, particularly when the dosage is titrated against the degree of pain.

The risk of respiratory depression is greatest for patients who are opioid naïve (e.g., patients who receive opioids for acute post-operative pain), whereas risk is minimized during chronic administration because patients rapidly develop tolerance to this effect. However, respiratory depression can occur in a patient with chronic pain if the pain is greatly reduced (e.g., following an ablation procedure) and the opioid dosage is not adjusted properly. Acute respiratory depression can be treated with an opioid antagonist, such as naloxone. Naloxone should be used with particular caution in patients who have received chronic meperidine therapy because it may precipitate seizures.

Opioid analgesics normally can be safely titrated upward in chronic-pain patients until pain is adequately controlled with minimal risk of respiratory depression. In fact, because respiratory depression is so rare in patients whose opioid dose has been titrated against pain, health care providers should explore alternative explanations (e.g., pneumonia, pulmonary embolism) if respiratory depression occurs in such a patient.

Sedation is another common adverse event associated with opioids. However, initial sleepiness after the implementation of a pain management regimen may result in part from the patient being exhausted from poor sleep during the time that the pain was not well controlled and finally being able to sleep because the pain is relieved. Sedation usually abates within the first days to weeks of therapy. During the initial period of opioid therapy, patients should be cautioned against driving or other activities that could be dangerous if sedation develops. However, with continued treatment, most patients are able to resume normal activities, even driving. Patients who are maintained on chronic opioid therapy for pain have been found to have driving performance similar to that of healthy controls receiving no medication, indicating that long-term opioid therapy does not impede psychomotor functions relevant to driving. In addition, patients who are opioid tolerant have been found to have no impairment in psychomotor abilities immediately after being given the opioid dose, no greater incidence of traffic accidents or violations, and no impairment noted on driving simulators. In fact, patient performance may be improved because the pain has been relieved. However, caution should be used, and if patients continue to feel sedated or to have other untoward effects, it may be wise to delay driving.

If sedation does not improve, treatment options include adding an adjuvant agent that will allow opioid dose reduction, switching to an alternate opioid or dosage route, or adding a stimulant such as dextroamphetamine or methylphenidate. Newer agents (e.g., modafinil, which is used in the treatment of narcolepsy) also may be useful for this purpose.

Like sedation, mild cognitive impairment manifested as confusion or delirium usually abates soon after initiation of therapy. If confusion or delirium persists for more than 2 weeks, it usually can be attributed to other factors. If opioid treatment appears to be the underlying etiology, treatment strategies are similar to those for sedation. Opioid dosages can be reduced with addition of an adjuvant agent, a trial with another opioid or dosage form may be effective, or treatment with a neuroleptic drug such as haloperidol may be attempted.

Although less common than other opioid adverse effects, pruritus can be a particularly bothersome adverse effect associated with opioids. It occurs more frequently with parenterally administered opioids than oral opioids. Tolerance to this adverse effect usually occurs quickly as well. However, if pruritus is severe or intolerable, naloxone can reverse the effect, regardless of the route of opioid administration. Antihistamines also are effective unless pruritus results from opioids administered intraspically. However, sedating antihistamines such as hydroxyzine and

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**Table 14. Treatment Strategies to Minimize Adverse Effects Associated With Opioids**

- Titrate dosages gradually.
- If a symptom occurs, determine its etiology (i.e., does it have another treatable source that is not related to the opioid?)
- Change dosing route or regimen.
- Switch to another opioid.
- Add an adjuvant and reduce the dosage.
- Add a drug to treat the effect.
- Eliminate other nonessential medications that may be contributing to the adverse event.
- Assume that constipation will occur and provide preemptive treatment.

*Source: Reference 15.*
diphenhydramine can intensify sedation that may occur with opioids. Switching opioids also may be beneficial.19

True allergy to opioids is rare. Some patients may believe that they have experienced an allergic reaction following adverse events such as nausea and vomiting or pruritus. Although these are not true allergic reactions, there have been reports of true anaphylactic-type allergic reactions with some opioids, including fentanyl, morphine, and meperidine.134,135 If a patient has developed opioid-induced anaphylaxis in the past and opioids are necessary to manage pain, an opioid from a different class should be selected. For example, a trial of fentanyl or methadone could be used in a patient with morphine allergy. In addition, skin-prick testing with different opioids can be performed to determine whether the patient can tolerate other opioids, as some cross-reactivity may occur. If anaphylaxis does occur, it can be partially attenuated with naloxone and/or antihistamines.134,135

Treatment with opioid antagonists is one possible strategy for reducing adverse events associated with opioids. However, treatment with opioid antagonists such as naloxone can reverse analgesia as well. Most opioid adverse events are mediated through opioid receptors in the periphery, while analgesia is mediated in the CNS. Therefore, an opioid antagonist that acts peripherally rather than centrally could theoretically reverse adverse effects while preserving analgesia.

Methylnaltrexone is an investigational opioid antagonist that does not cross the blood-brain barrier but is active peripherally. Methylnaltrexone has been found to decrease adverse effects associated with morphine, including delayed gastric emptying, nausea and vomiting, and urinary retention, while maintaining the central analgesic effect of the opioid.136 In one study, opioid-induced constipation was rapidly reversed in 22 volunteers.137 In more than 90% of subjects, relief from constipation came within 1 minute of a methylnaltrexone IV infusion.138,139 Phase III clinical trials of methylnaltrexone were under way in 2004.

**Adjuvant and Other Medications**

While traditional analgesics are the mainstay of pharmacologic therapy for many patients, a number of chronic painful conditions, especially neuropathic conditions, respond well to treatment with adjuvant medications. Guidelines for the treatment of neuropathic pain recommend gabapentin, the 5% lidocaine patch, and TCAs as first-line treatments in addition to opioid analgesics and tramadol.140

As with NSAIDs and opioids, failure to achieve an adequate response to one agent does not necessarily mean that patients will fail to respond to another. Patients may have variable responses to different agents among and within classes. Individual patients may benefit from agents that have fewer equivocal supporting data from randomized, controlled clinical trials.

**Antiepileptic Drugs**

Antiepileptic drugs (AEDs) have been demonstrated to be effective for treating a variety of neuropathic pain states. AEDs reduce cell membrane excitability in neurons, thereby suppressing pathologic action potentials. However, it appears that they also have analgesic effects that are not directly related to this activity.15 Other types of drugs that suppress seizures do not affect pain, and not all AEDs that are effective for epilepsy are effective for pain.15 AEDs are often recommended for treating lancinating pain—pain characterized by the patient as “shooting” or “stabbing.”15

Carbamazepine, phenytoin, gabapentin, and lamotrigine have been evaluated for their effects on neuropathic pain in randomized, controlled clinical trials.141 Gabapentin, the first AED to receive FDA approval for treating neuropathic pain, has demonstrated efficacy in clinical trials of patients with postherpetic neuralgia, painful diabetic neuropathy, mixed neuropathic pain syndromes, phantom limb pain, Guillain-Barré syndrome, and acute and chronic pain from spinal cord injuries.140 Carbamazepine is approved for trigeminal neuralgia, and valproate is approved for migraine prophylaxis.15 Due to side effects, newer AEDs (e.g., gabapentin, lamotrigine) are now used preferentially over the older agents for the management of neuropathic pain.

The AEDs have somewhat different mechanisms of action; therefore, failure to respond to one agent does not necessarily predict a poor response to other AEDs. Trials with AEDs should be initiated with a low dose administered at bedtime, and gradually titrated upward over a period of 4 to 8 weeks.141 These medications do not have a ceiling dose; rather, dosages are limited by the incidence of adverse events. Dosages should be titrated upward until adverse events appear, and then reduced to the dosage at which adverse events did not occur.

Adverse events associated with AEDs vary among the agents. The most common class effects are sedation, mental clouding, dizziness, nausea, and unsteadiness.13 Older AEDs also are associated with a risk of rash, hypersensitivity, and hepatic dysfunction, and certain agents require ongoing monitoring of affected parameters.

The investigational AED pregabalin shows promise for the treatment of pain. It has demonstrated analgesic efficacy and tolerability in animal models of nociceptive and neuropathic pain and in human studies of patients with postherpetic neuralgia and painful diabetic neuropathy.142 Like gabapentin, pregabalin is a structural analog of GABA, and is more rapidly absorbed. In addition, pregabalin does not appear to require the lengthy titration period needed for other AEDs.142

Other AEDs that are being investigated for their utility in treating neuropathic pain include oxcarbazepine, tiagabine, vigabatrin, and zonisamide.141

**Antidepressants**

Antidepressants have been found to be effective for treating a variety of pain states. Their efficacy for treating pain does not result directly from their efficacy for treating depression; patients experience similar degrees of analgesia regardless of whether they are also depressed. TCAs block the reuptake of both norepinephrine and serotonin, whereas the selective serotonin reuptake inhibitors (SSRIs), as their name implies, only block the reuptake of serotonin. Blockade of norepinephrine reuptake in the CNS stimulates endogenous pain modulation through descending spinal pathways, and serotonin reuptake blockage seems to enhance this effect.15,143 However, serotonin blockade alone does not appear sufficient to produce analgesic effects, which explains why SSRIs appear less efficacious in treating neuropathic pain states.143 TCAs also appear to have a variety of analgesic properties that extend beyond their modulation of serotonin and norepinephrine.144

TCAs are used to treat headaches (including migraines), low back pain, fibromyalgia, painful diabetic neuropathy, postherpetic neuralgia, central pain, and cancer pain. TCAs appear to be most effective for treating burning pain or hypersensitivity, but also may be beneficial for lancinating neuropathic pain. TCAs appear to be relatively similar in efficacy to AEDs for managing neuropathic pain.15 Approximately 30% of patients will experi-
ence a 50% reduction in pain. Amitriptyline appears to have the greatest analgesic effect of the TCAs, but is also associated with the greatest incidence of adverse events. TCAs have more clearly demonstrated efficacy than SSRIs, but their use is limited by a greater incidence of adverse events. Class effects of TCAs include sedation, orthostatic hypotension, and anticholinergic effects. Elderly patients are more prone to experiencing these adverse events. Bedtime administration may help alleviate the impact of some of these effects. On the other hand, if the patient experiences insomnia as an adverse event, daytime administration is recommended. The secondary amines (e.g., nortriptyline and desipramine) are generally preferred because they have a reduced risk for sedation, orthostatic hypotension, and anticholinergic effects.

Clinical trial data supporting the use of SSRIs are more mixed. These agents are generally regarded as second-line treatments for patients who cannot tolerate TCAs. However, newer antidepressants that inhibit reuptake of both serotonin and nor-epinephrine appear to have a greater potential role in pain management. Venlafaxine is a newer antidepressant that inhibits reuptake of both serotonin and norepinephrine but is not associated with as many adverse events as the TCAs. Some evidence suggests that this agent may be more effective than traditional SSRIs for treating neuropathic pain. In one study of patients with painful polyneuropathy, venlafaxine was as effective as the TCA imipramine; both treatments were more effective than placebo.

Duloxetine, a second serotonin and norepinephrine reuptake inhibitor, was approved for the treatment of depression in August 2004 and for pain associated with diabetic neuropathy in September 2004. Additional data suggest that it is effective for the treatment of fibromyalgia. In one study, duloxetine treatment improved fibromyalgia symptoms and pain severity independently from effects on mood. (Duloxetine also may be used in the treatment of stress urinary incontinence.)

Local Anesthetics
Local anesthetics often are used in the management of neuropathic pain. Two products are currently available for this use: EMLA cream (eutectic mixture of local anesthetics), which contains lidocaine and prilocaine, and a 5% lidocaine patch. EMLA is more widely used for venipuncture and cutaneous biopsy. The 5% lidocaine patch has been shown to be effective for treatment of peripheral neuropathic pain, and is FDA approved for the treatment of postherpetic neuralgia. One study suggests that the 5% lidocaine patch also is effective for the treatment of knee pain resulting from osteoarthritis.

Systemic administration of local anesthetics (e.g., lidocaine, mexiletine, tocainide) appears effective for a variety of different types of acute pain (postoperative pain, burn pain, cancer pain) and a variety of neuropathic pain states (diabetic neuropathy, postherpetic neuralgia, phantom limb pain, radiculopathy, and others).

Antianxiety Agents
In chronic pain, benzodiazepines may produce analgesic effects by reducing the anxiety associated with the chronic-pain state and the resulting insomnia and muscle tension that contribute to pain. In addition to these uses, they are used as anti-convulsants and antispasmodics for treating neuropathic pain. Although clinical trial data are sparse, conditions that may benefit from benzodiazepines include chronic tension headache, temporomandibular joint dysfunction, trigeminal neuralgia, phantom limb pain, opioid-induced myoclonus, paroxysmal postlaminectomy pain, and posttraumatic neuralgias. However, benzodiazepines can cause cognitive impairment and physical dependence, and can worsen preexisting depression. They also produce additive CNS depressant effects when combined with an opioid. Thus, caution must be used when administering these agents, and their long-term use is controversial.

Clonazepam often is the preferred agent because it can be dosed once daily at bedtime, which helps avoid daytime sedation.

Skeletal Muscle Relaxants
Skeletal muscle relaxants (SMRs) are beneficial for a variety of pain states that involve muscle spasms. These agents interrupt the pain-spasm-pain cycle without affecting muscle function. This effect provides an improved range of motion, helps patients return to their prior functional status, and facilitates the initiation of rehabilitation and therapeutic exercise. These agents are chemically diverse and they do not have well-defined mechanisms of action, but all appear to derive their effects from central rather than peripheral actions.

Currently available SMRs include baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, diazepam, metaxalone, methocarbamol, orphenadrine, and tizanidine. These agents are commonly used for the treatment of acute traumatic muscle spasms for a period limited to 2 or 3 weeks, which coincides with the time period associated with painful acute muscle spasms. SMRs have demonstrated efficacy for treating muscle spasms in cervical and lumbar regions, and temporomandibular disorder. The data supporting their use for other disorders are more limited. However, baclofen (which is a chemical analog of GABA) is indicated for treating painful spasticity associated with multiple sclerosis and also has been shown to be effective for treating neuropathic pain caused by certain neuralgias and ophthalmic-postherpetic neuralgia.

Adverse events associated with SMRs include drowsiness, dizziness, light-headedness, fatigue, and sedation. Some agents also are associated with GI and anticholinergic adverse events. There are a few case reports of misuse of carisoprodol and meprobamate.

Capsaicin
Capsaicin is an enzyme that has been isolated from hot chili peppers. Topical application of capsaicin cream depletes substance P from sensory C fibers, producing analgesia after repeated application. It has been found to significantly reduce pain in a number of localized painful conditions and is indicated for the treatment of minor aches and pains of muscles and joints associated with simple backache, arthritis, strains, bruises, and sprains. It also appears effective for treating localized neuropathic conditions, such as postherpetic neuralgia.

Many patients experience temporary burning or stinging following application of capsaicin cream, which is a result of the mechanism of action of the product. This effect usually abates after a few days or weeks of treatment, and coincides with the development of analgesia as substance P is depleted. However, it also can lead to problems with adherence, because capsaicin must be applied four to five times daily for a few weeks before relief is obtained, and the burning experienced during this period can be a deterrent to treatment. Patients should be advised to thoroughly wash their hands after each application so that they do not inadvertently apply capsaicin to other areas, causing burning.

Tramadol
Tramadol is a weak opioid agonist that is effective for treating...
moderate to moderately severe pain.\textsuperscript{78,155} Its mu-receptor binding affinity is 10-fold less than that of codeine and 6,000-fold less than that of morphine.\textsuperscript{78} The primary metabolite has a 200-fold greater affinity for the mu opioid receptor than tramadol itself, and appears to be partially responsible for the efficacy.\textsuperscript{156} In addition to its weak opioid properties, tramadol inhibits reuptake of serotonin and norepinephrine at the level of the dorsal horn.\textsuperscript{155}

The most common adverse events associated with tramadol are dizziness, nausea, constipation, and somnolence, and these events are not fully reversible with naloxone.\textsuperscript{43} Compared with other opioids, tramadol carries a reduced risk of respiratory depression with overdose and a low risk of physical dependence and abuse, and is a federally nonscheduled opioid analgesic.\textsuperscript{78,157} Tramadol also carries a small risk for seizures, which occur in about 2 of 100,000 patients. This risk appears to be increased in patients who exceed the recommended dose and those who have epilepsy or take other medications that reduce the threshold for seizures.\textsuperscript{155,158}

**Corticosteroids**

Corticosteroids are powerful anti-inflammatory agents that reduce nociception. They increase production of phospholipase A\(_2\), which inhibits production of prostaglandins from arachidonic acid, and have a number of additional anti-inflammatory effects.\textsuperscript{141} Corticosteroids often are used in managing tumor-related pain, and have several other specialized uses in treating patients with cancer.\textsuperscript{43} Intra-articular injection of corticosteroids also is useful for treatment of chronic inflammatory joint pain.\textsuperscript{141}

Chronic administration of systemic corticosteroids produces a variety of known adverse effects, including weight gain, osteoporosis, Cushing’s syndrome, and other effects mediated by the hypothalamic-pituitary-adrenal axis. Corticosteroids produce a fivefold increased risk of GI bleeding when coadministered with NSAIDs, as well as an increased bleeding risk with anticoagulants.\textsuperscript{45} Because of these effects, systemic corticosteroid treatment often is reserved for those who are terminally ill, or should be limited to 1 to 2 weeks of therapy.

Articular and periarticular injections of corticosteroids are widely used for patients suffering from conditions such as tendinitis, bursitis, tenosynovitis, and epicondylitis. These injections also have been shown to reduce inflammation in rheumatoid arthritis, to have a disease-modifying effect in osteoarthritis, and to reduce symptoms of neuropathic pain.\textsuperscript{159} The corticosteroid may be combined with a local anesthetic. Infection of the intended site of injection is an absolute contraindication to corticosteroid administration.\textsuperscript{159}

**Botulinum Toxins**

Botulinum toxins (BTX) are neurotoxins that block acetylcholine release in neuromuscular synapses, producing paralysis. Several subtypes have been identified, including A, B, C, D, E, F, and G. Botulinum toxin subtype A (BTA) and botulinum toxin subtype B (BTB) are commercially available in the United States. In addition to paralyzing muscle fibers, animal studies suggest that BTX seems to have independent analgesic effects that include anti-inflammatory actions, blocking release of gluta-mate, and reducing substance P concentrations. BTA was first approved for the treatment of strabismus (i.e., crossed eyes) in 1989.\textsuperscript{160} Additional research indicated that BTA would be effective for conditions characterized by muscle hyperactivity, such as spasmodic torticollis and cervical dystonia.

More recent trials have found efficacy for BTX in the treatment of myoclonus, tension-type headache, trigger points, myofascial pain, back pain, and other focal dystonias and spastic disease states.\textsuperscript{161,162} BTX is primarily reserved for the treatment of patients who are refractory to other treatments. Often, BTX can interrupt the pain-spasm-pain cycle for at least 3 months, a time frame long enough for benefits from other therapeutic modalities (e.g., physical therapy) to be achieved.\textsuperscript{163}

**NMDA Antagonists**

NMDA receptors are located throughout the spinal cord and are involved in chronic nociceptive and neuropathic pain. Repetitive C fiber stimulation can activate NMDA receptors, resulting in the sensitization of wide dynamic range neurons and the wind-up phenomenon. Experimental evidence suggests that medications that reduce the activation of NMDA receptors, including amantadine, memantine, ketamine, and dextromethorphan, may be useful as analgesic agents.

Studies have shown analgesic efficacy for dextromethorphan in the treatment of neuropathic pain and the development of tolerance to morphine, and as preemptive analgesia for patients undergoing tonsillectomy.\textsuperscript{163} However, dosages required to produce analgesic effects are several times greater than those required for antitussive effects.\textsuperscript{143} Raising dosages increases the risk for a variety of adverse events.

Amantadine, which is used as an antiviral and antiparkinsonian agent, has a relatively low risk of adverse events. One clinical trial found it to reduce neuropathic pain in patients undergoing surgery for cancer.\textsuperscript{163} Memantine, which is used for treating Alzheimer’s disease, has been found to be effective for treating several forms of neuropathic pain in animal models.\textsuperscript{164}

Ketamine has been used in the treatment of neuropathic pain, as a coanalgesic in patient-controlled analgesia, and as a preemptive analgesic agent.\textsuperscript{143} As noted earlier, methadone also derives part of its analgesic efficacy from activity as an NMDA antagonist.

Some NMDA antagonists (e.g., dextromethorphan, ketamine) may be misused by patients for their dissociative effects.

**Marijuana**

Cannabinoids, which are found in marijuana, have multiple effects on biologic systems. The cannabinoid-receptor system appears to play an important role in the transmission and modulation of pain, and there is a reasonable body of evidence documenting the antinociceptive effects of cannabinoids.\textsuperscript{165} The use of medical marijuana remains controversial, both for sociopolitical reasons and for safety concerns about smoking as a drug delivery system. Although some states have made it legal for patients to use marijuana for medical purposes, including the treatment of pain, federal law still prohibits medical marijuana.\textsuperscript{165,166}

The Drug Enforcement Administration provides information on its Web site stating that “medical marijuana already exists. It’s called Marinol.” Marinol® (dronabinol) is a cannabinoid that is indicated for anorexia associated with weight loss in patients with AIDS, and for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.\textsuperscript{166} Dronabinol is not an analgesic. However, in one survey of Californians who used marijuana for medical reasons, 40% did so for the treatment of chronic pain.\textsuperscript{167} Thus, dronabinol does not meet the needs of many patients who use medical marijuana. Additional research is under way in an attempt to develop pharmaceutical cannabinoids with wider clinical applications.
Considerations for Special Populations

In addition to treatment considerations for patients with hepatic and renal impairment or other comorbid diseases discussed above, special consideration must be given to pain management in children, the elderly, cognitively impaired adults, and those with past or current addiction.

Pain may be more difficult to assess in young children and elderly patients, especially those with cognitive impairment, delirium, or dementia, and those who are nonverbal. These patients have obvious difficulties in effectively communicating information about the severity of their pain and often are particularly vulnerable to undertreatment. Concerns about the potential misuse of medications complicate the treatment of patients with a social history that includes addiction. Pharmacists and other health care providers have an obligation to ensure that these patients receive appropriate assessment and management of their pain.

Children

Although it was once believed that infants and children do not experience pain to the same degree as adults because of immature nervous systems, research in the past two decades demonstrates that even late-gestation fetuses experience pain. Research has shown that neonates have physiologic and hormonal responses to pain that are similar to those seen in adults.168

Thus, it should be assumed that anything that would be painful for an adult would be painful for a child or infant. According to a joint policy statement of the American Academy of Pediatrics and the American Pain Society, pain management strategies for children should be considered even for simple medical procedures (e.g., venipuncture) or for acute illnesses (e.g., otitis media).169 They also state that when pain is associated with surgery or trauma, the child should be discharged with a plan for addressing pain management at home.169

Appropriate assessment of pain in children differs from that for adults, based on the cognitive abilities of the child to report pain. However, tools are available for the assessment of pain in every age group, even premature infants, and providers should attempt to assess the presence and severity of pain in all patients. For example, the Wong-Baker FACES Pain Rating Scale discussed earlier is particularly useful for young children.

The risks and benefits of various pain management strategies for children must be considered on an individual basis. Appropriate interventions range from deep sedation and anesthesia to teaching the child coping mechanisms, such as the use of imagery and relaxation. Pharmacologic treatment may include acetaminophen, NSAIDs, opioids, and/or local anesthetics. In addition, efforts to reduce distress in parents also are beneficial, as children are more likely to be anxious if their parents seem upset.

Dosing requirements for children are different from those for adults. The dosage determination should include consideration of body weight, physiologic development, and the medical situation. Clinical effects and pharmacokinetics of opioids in children at least 6 months of age are similar to those in adults, and dosages should be calculated according to weight.43 Infants less than 6 months of age, especially those who are premature or ill, have decreased hepatic and renal function and may experience delayed toxicity, and respiratory depression is more likely. In such children, one quarter to one third of the recommended starting dose based on weight for older children should be used, and then titrated to effect. Infants should be very closely monitored for adverse effects, particularly respiratory depression.43

Other medications taken by the child also must be considered, as there is a potential for synergistic effects between analgesics, anxiolytics, antihistamines, and antiemetics. Regarding the long-term use of opioids in children, the American Academy of Pediatrics and the American Pain Society state that dosages should be adjusted as necessary to accommodate the development of physical tolerance and that, upon discontinuation, children should be gradually weaned from opioids to avoid withdrawal symptoms.169

Elderly and Cognitively Impaired Patients

Many painful conditions, such as arthritis, are very common in the elderly. Unfortunately, many patients consider such pain to be a “normal” part of aging. While many painful conditions increase in prevalence in older individuals, such conditions should not simply be accepted as a part of aging, and should be appropriately managed.

Assessing cognitive status is an important component of the overall approach to treating pain in elderly patients. Standard rating scales require patients to assign an abstract number to the pain that they feel and communicate that information to another person. Many cognitively impaired elderly individuals have difficulty performing these conceptual tasks. Thus, care providers should ensure that a patient understands a rating scale before relying on it to guide treatment decisions.

As with children, simplified versions of such ratings scales that allow patients to match the intensity of their pain to pictures may be useful. However, even simplified pain assessment scales may not be practical for older adults with moderate to severe mental impairment or for those who are nonverbal. Providers must look to nonverbal cues that suggest pain in such patients and seek input from family and caregivers. The American Geriatrics Society Panel on Persistent Pain in Older Persons has identified several nonverbal cues of pain in cognitively impaired elderly individuals (Table 15). The American Geriatrics Society panel called for an initial assessment and regular reassessment of pain using the same rating scale (where feasible) for each assessment to track changes in pain severity and the impact of treatments.

An increased risk of adverse events with medications in the elderly contributes to the reluctance to aggressively manage pain in this population. Although greater caution should be used, adequate analgesia often can be provided.

Hepatic and renal function are often reduced in elderly individuals, which results in a greater peak plasma concentration and longer half-life for many medications. For example, those with a creatinine clearance of less than 60 mg/dL generally experience peak plasma concentrations that are 20% to 50% higher than normal. Consequently, elderly patients often require smaller dosages than their younger counterparts. As a general rule, “start low and go slow” is a wise approach for pharmacotherapy of the elderly. Initial dosages should usually be one third to one half of those used in younger patients, and should be titrated upward more gradually. In addition, controlled-release forms of drugs should be used more cautiously because of the greater risk for drug accumulation.

Acetaminophen up to 4,000 mg per daily can generally be used safely in the elderly; however, NSAIDs have an increased risk of GI bleeding in this patient population. NSAIDs are also more likely to produce renal toxicity, particularly in patients who
Table 15. | Behaviors Suggestive of Pain in Patients Who Have Difficulty Communicating

<table>
<thead>
<tr>
<th>Type of Behavior</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial expressions</td>
<td>Slight frown, sad or frightened face</td>
</tr>
<tr>
<td></td>
<td>Grinning, wrinkled forehead, close or tightened eyes</td>
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<tr>
<td></td>
<td>Any distorted expression</td>
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<tr>
<td></td>
<td>Rapid blinking</td>
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<tr>
<td>Verbalizations</td>
<td>Sighing, moaning, groaning</td>
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<tr>
<td></td>
<td>Calling out</td>
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<tr>
<td></td>
<td>Noisy breathing</td>
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<tr>
<td></td>
<td>Asking for help</td>
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<tr>
<td></td>
<td>Verbally abusive</td>
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<tr>
<td>Body language</td>
<td>Rigid, tense, or guarded</td>
</tr>
<tr>
<td></td>
<td>Fidgeting, pacing, rocking</td>
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<tr>
<td></td>
<td>Altered mobility</td>
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<tr>
<td>Interpersonal interactions</td>
<td>Aggressive or combative</td>
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<tr>
<td></td>
<td>Decreased socialization</td>
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<tr>
<td></td>
<td>Withdrawn</td>
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<tr>
<td>Changes in daily activities</td>
<td>Appetite change</td>
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<tr>
<td></td>
<td>Changes in patterns of sleep or rest</td>
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<tr>
<td></td>
<td>Sudden change in common routine</td>
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<td></td>
<td>Increased wandering</td>
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<tr>
<td>Mental status</td>
<td>Crying</td>
</tr>
<tr>
<td></td>
<td>Increased confusion</td>
</tr>
<tr>
<td></td>
<td>Irritability or distress</td>
</tr>
</tbody>
</table>

Source: Reference 170.

Patients With Past or Current Substance Abuse

Several medications used in the management of pain (e.g., opioids, NMDA antagonists, certain SMRs) may be misused or diverted. Thus, health care professionals must take care when prescribing these medications in order to avoid harm to patients, to protect the public health, and to avoid potential legal, regulatory, or licensing penalties.172 These issues are particularly salient if the patient has a history of past or current substance abuse.

All patients who are candidates for treatment with potentially addictive substances should be questioned about their current and past use of licit and illicit drugs, including alcohol and nonprescription medications (e.g., dextromethorphan).16 A past history of drug or alcohol misuse or addiction is not a contraindication to the treatment of pain with opioids if indicated; however, some state laws may place limitations on this practice. An appropriate treatment plan with tight boundary setting should be agreed upon before writing the first prescription. If the patient is actively suffering from an addictive disorder, prescription of controlled substances to treat chronic pain may be contraindicated, and treatment of the addictive disorder should be implemented, possibly in conjunction with treatment of the pain condition.26 Such patients should be treated by specialists in pain management and addictionology. (However, controlled substances may be appropriate for treating acute pain in actively addicted individuals.36)

Appropriate limitations and boundary setting for patients may vary by the clinical situation. For example, less strict limit setting may be appropriate for patients who are terminally ill or who are experiencing acute posttrauma pain than for those with chronic nonmalignant pain. A number of boundary-setting strategies exist, including informed consent for chronic opioid therapy and medication therapy management agreements (sometimes referred to as "opioid contracts"). Many university pain treatment centers and pain management specialists advocate implementing such controls for all patients who use opioids for chronic nonmalignant pain.36 Requiring all appropriate patients to sign such agreements reduces the stigma associated with the agreement, can improve the provider-patient relationship, and can reduce the potential risks associated with prescribing controlled substances.36 Many such agreements require that patients receive all their controlled substance prescriptions from one prescriber and one pharmacy. Thus, it is important for pharmacists to know which of their patients have these agreements in place. Ideally, a copy of the agreement should be maintained in the patient’s record at the pharmacy.

Additional information about the potential for misuse and diversion and appropriate strategies to manage these risks can be found in the resources listed in the Appendix.

Interventional and Surgical Therapies

Dozens of interventional techniques are used in pain management. These techniques may include peripheral nerve blocks, epidural steroid injections, spinal cord or brain stimulation, nerve route blockades, and others. Such procedures usually are performed by a pain specialist or anesthesiologist and often are used as part of a multidisciplinary approach to pain management.
While many types of pain can be managed with noninvasive treatments, surgery may be the best approach for some patients. Surgery is more common for pain with orthopedic causes—such as a total knee replacement for severe arthritis of the knee. A number of neurosurgical procedures also are used, including neurolysis (destruction of neural tissue with chemicals, heat, or cold), neuroaugmentation (disruption of neural signals), and neuroablation (destruction of nerves associated with the pain). Numerous other forms of surgery also are used in an attempt to manage pain.15

Conclusion

Pain management is an important component of the treatment provided to patients in a wide variety of health care settings. Regardless of the etiology or duration of the condition, all pain should be assessed and a treatment plan developed. The treatment plan for each patient should be individualized based on the individual needs and goals of the patient, as well as the patient’s responses to treatments. Optimal management of pain usually requires a multimodal approach that combines both nonpharmacologic and pharmacologic treatments. Patients with chronic pain often require treatment by a multidisciplinary team to maximize their function and quality of life.

Pharmacotherapy is an important component of the pain management program for many patients. As the medication experts, pharmacists play an important role in educating patients and other health care providers about the optimal use of available agents. Pharmacists often provide invaluable information to prescribers about the clinical effects of and treatment considerations for available medications, and can help guide medication selection, titration, and conversion. Pharmacists educate patients about proper usage of their medications, and provide guidance and support to patients undergoing treatment for pain. In addition, pharmacists play an important role in monitoring for adverse events, and helping patients anticipate and manage adverse events.

Appendix | Pain Management and Pharmaceutical Care Resources

**Associations and Societies**

American Academy of Pain Medicine  
http://www.painmed.org

American Chronic Pain Association  
http://www.theacpca.org

American Pain Society  
http://www.ampainsoc.org

American Society of Addiction Medicine  
http://www.asam.org

The American Society of Law, Medicine & Ethics  
http://www.aslme.org

International Association for the Study of Pain  
http://www.iasp-pain.org

**Additional Educational Resources**

City of Hope, Pain/Palliative Care Resource Center  
http://www.cityofhope.org/prc

Dannemiller Memorial Educational Foundation  
http://www.pain.com

National Pain Education Council  
http://www.npecweb.com

Partners Against Pain  
http://www.partnersagainstpain.com

Pharmacist.com  
http://www.pharmacist.com

University of Wisconsin–Madison Pain and Policy Studies Group  
http://www.medsch.wisc.edu/painpolicy

**Recommended Reading**


**Online Patient Assessment Tools**

Brief Pain Inventory  

Initial Pain Assessment Tool  

McGill Pain Questionnaire  
http://www.hsrq.ann-arbor.med.va.gov/creme(section2).pdf

Continued on next page
Appendix | Pain Management and Pharmaceutical Care Resources (continued)

Opioid Therapy Documentation Kit

Oswestry Disability Index
http://www.drridgway.ca/pdfs/Oswestry.pdf

Pediatric Pain Assessment Tools
http://www.anes.ucla.edu/pain/assessment_tools.html

COMPLEMENTARY AND ALTERNATIVE MEDICINE AND DIETARY SUPPLEMENT RESOURCES


RESOURCES RELATED TO MISUSE AND ABUSE OF CONTROLLED SUBSTANCES


Substance Abuse and Mental Health Services Administration
http://www.samhsa.gov

University of Wisconsin–Madison Pain and Policy Studies Group
http://www.medsch.wisc.edu/painpolicy

Sample Medication Management Agreements for Chronic Opioid Therapy
American Academy of Pain Medicine
http://www.painmed.org/productpub/statements/pdfs/controlled_substances_sample_agrmt.pdf

Oregon Health and Science University
http://www.ohsu.edu/ahec/pain/med_contractlf.pdf

Sample Informed Consent Forms for Chronic Opioid Therapy
American Academy of Pain Medicine

Oregon Pain Society
http://www.painsociety.com/material_risk.pdf

Continuing Education Programs
American Pharmacists Association
http://www.pharmacist.com

- Controlled Substance Prescriptions and Pain Management: Striking a Balance
- Implementing Pain Management Services in Pharmacy Practice
- Pharmacists’ Responsibilities in Managing Opioids: A Resource
71. Slattery JT, Nelson SD, Thummel KE. The complex interaction between ethanol and


Assessment Questions

INSTRUCTIONS: For each question, circle the letter on the C.E. Examination Form corresponding to the correct answer. Please review all of your answers to be sure you have circled the proper letter. There is only one correct answer to each question.

1. Allodynia is defined as:
a. The absence of pain from a stimulus that would normally cause pain.
b. Pain resulting from a stimulus that does not normally cause pain.
c. An increased pain response to a stimulus that normally causes pain.
d. Abnormal sensations resulting from nerve damage.

2. Pain is defined as:
a. An unpleasant sensation associated with actual or potential tissue damage.
b. An unpleasant emotional experience.
c. Both a and b.
d. None of the above.

3. Transduction is:
a. Afferent transmission of pain signals to the dorsal horn.
b. Stimulation of nociceptors in the periphery leading to the generation of action potentials.
c. Pain transmitted by myelinated A-delta fibers.
d. Modulation of pain through descending pathways.

4. “Wind-up” pain occurs when:
a. Prolonged pain signals create central sensitization to pain signals.
b. Comorbid anxiety and depression enhance the pain response.
c. NMDA receptors are antagonized.
d. Prostaglandins are synthesized from arachidonic acid.

5. In the “Pain in America” survey, what percentage of patients with chronic pain reported that they had to move to a residence that was easier to care for as a result of their pain?
a. 3%.
b. 7%.
c. 13%.
d. 23%.

6. Why might chronic pain make it difficult for patients to maintain interpersonal relationships?
a. Pain interferes with sleep, making patients irritable and difficult to be around.
b. Patients may no longer be able to engage in regular social activities.
c. Patients may become depressed or develop other psychological comorbidities.
d. All of the above.

7. Approximately what percentage of Americans report that they experience nonmigraine headaches each year?
a. 53%.
b. 73%.
c. 82%.
d. 90%.

8. Unrelieved pain is associated with all of the following physical effects except:
a. Desensitization of nociceptors.
b. Impaired immune function.
c. Cardiovascular adverse outcomes including unstable angina, MI, and deep vein thrombosis.
d. Decreased GI function.

9. The assessment of pain should include all of the following except:
a. The patient's subjective rating of the severity of pain.
b. A description of the functional impact of pain on the patient.
c. Use of placebos to determine whether the patient is being honest about his or her pain reports.
d. Information about the patient's family and psychosocial history.

10. Establishing a diagnosis for the source of the pain is important because:
a. Curative treatments should be used for many painful conditions.
b. Establishing a diagnosis can help guide the appropriate selection of treatment strategies.
c. Pain should not be treated until a definitive diagnosis is made.
d. Both a and b.

11. Goal setting in pain management may include all of the following except:
a. A discussion of the degree of pain relief that patients may be able to expect.
b. Establishing functional goals that the patient wants to achieve.
c. Maintaining analgesic dosages below a certain level.
d. Improving the patient’s quality of life.

12. Palliative care should be used:
a. When a physician certifies that a patient has less than 6 months to live.
b. At any time during a serious illness.
c. When the patient agrees to forgo any further curative treatments.
d. When the patient has cancer.

13. If physical dependence occurs in a patient who is receiving long-term opioid therapy, it means that:
a. The patient has become addicted and should be referred to a drug treatment program.
b. The patient has lost control over his or her use of the medication and treatment should be discontinued.
c. The patient is having a normal physiological response to the medication and will experience a withdrawal syndrome if the medication is stopped or quickly decreased.
d. The patient has become tolerant to the drug and the dosage should be increased.

14. Continuous low-level heat for low back pain:
a. Produces vasodilation that increases tissue perfusion.
b. Can help relax muscles and reduce muscle spasms.
c. Has been shown in clinical trials to be more effective than acetaminophen 4,000 mg/day or ibuprofen 1,200 mg/day.
d. All of the above.

15. Which of the following statements about TENS is false?
a. The analgesia produced by TENS can be partially reversed with naloxone.
b. TENS produces analgesia similar in magnitude to that of acetaminophen with codeine.
c. TENS takes advantage of the wind-up theory of pain.
d. TENS takes advantage of the gate-control theory of pain.
16. Acupuncture is said to:
   a. Interfere with the transmission of painful nerve impulses by inhibiting nerves that are stimulated by needles.
   b. Rebalance the circulation of Qi through the body’s meridians.
   c. Be a leading cause of community-acquired methicillin-resistant Staphylococcus aureus infections.
   d. All of the above.

17. According to the Dietary Supplement and Health Education Act of 1994, dietary supplements sold in the United States:
   a. Must have their safety and efficacy reviewed by the FDA prior to marketing.
   b. Must be manufactured according to good manufacturing practices.
   c. Only have their safety reviewed by the FDA prior to marketing approval.
   d. None of the above.

18. Which dietary supplements should be “UPA free”?
   a. Glucosamine and chondroitin.
   b. Alpha lipoic acid.
   c. Butterbur root.
   d. Avocado soybean unsaponifiables.

19. Conditions that increase the risk for hepatotoxicity with acetaminophen include all of the following except:
   a. Hepatic dysfunction.
   b. Alcoholism.
   c. Concomitant use of medications that induce cytochrome P-450 3A4.
   d. Fasting.

20. Approximately what percentage of patients who use nonselective NSAIDs are hospitalized for serious upper GI adverse effects?
   a. 0.2%.
   b. 0.8%.
   c. 1%–2%.
   d. 2%–4%.

21. Which of the following is not an adverse event associated with NSAID use?
   a. Renal toxicity.
   b. Deep vein thrombosis.
   c. Hepatic dysfunction and necrosis.
   d. Cognitive impairments.

22. Strategies that can be used to reduce the risk of GI irritation with aspirin and other NSAIDs include all of the following except:
   a. Coadministration with misoprostol, proton pump inhibitors, or double doses of H2-receptor antagonists.
   b. Administering the medication with food.
   c. Using NSAIDs such as aspirin and indomethacin that are potent inhibitors of COX-1.
   d. Using enteric-coated or buffered products.

23. Recent data suggest that available COX-2 selective NSAIDs:
   a. Increase the incidence of GI adverse events compared with nonselective NSAIDs coadministered with misoprostol.
   b. Retain the antiplatelet effects of nonselective NSAIDs.
   c. May have adverse cardiovascular effects.
   d. All of the above.

24. Which of the following statements about tramadol is false?
   a. It is a nonscheduled opioid analgesic.
   b. Its analgesic efficacy results from both the parent compound and an active metabolite.
   c. Its analgesic effects are reversed by naloxone.
   d. It inhibits reuptake of serotonin and norepinephrine at the dorsal horn.

25. Opioids are effective and appropriate analgesics for the treatment of:
   a. Somatic and visceral pain.
   b. Certain types of neuropathic pain.
   c. Constipation pain.
   d. Both a and b.

26. Patients with chronic persistent pain should generally receive medication:
   a. Around the clock with a controlled-release formulation plus an immediate formulation for breakthrough pain.
   b. As needed with a controlled-release formulation plus an immediate formulation for breakthrough pain.
   c. Around the clock with an immediate-release formulation.
   d. As needed with an immediate-release formulation.

27. Which of the following statements about selecting among available routes of administration for opioids is false?
   a. The IM route is generally preferred for acute pain because it produces predictable pharmacokinetics.
   b. The least invasive route(s) should be used.
   c. Parenteral or rectal opioids are options for patients who have difficulty swallowing.
   d. All of the above.

28. When analgesia is sufficient but an opioid switch is being made as a result of intolerable adverse effects, the general rule for health care providers to follow is:
   a. Rely on equianalgesic dosing tables for definitive guidance about appropriate dosage selection.
   b. Dose the new opioid at 50% to 75% of the equianalgesic dosage and then modify the dosage based on clinical response.
   c. Taper off the first opioid, initiate the second opioid using the initial starting dose, and then titrate to effect.
   d. None of the above.

29. Which of the following statements about methadone is false?
   a. It interacts with both opioid receptors and NMDA receptors.
   b. It has a toxic metabolite that can accumulate.
   c. It has an elimination half-life of about 30 hours and can accumulate with repeated dosing.
   d. Opioid conversion to methadone can be easily performed using equianalgesic data as a guide.

30. Dosages for pure opioid analgesics:
   a. Should be titrated based on individual response up to the maximum dosage listed in the product labeling.
   b. Should be titrated based on individual response with no ceiling dosage.
   c. Should initially be halved for patients with nonmalignant pain.
   d. Should be initially doubled for patients with renal dysfunction.

31. Which of the following controlled-release opioids is available in a dosage form that can be opened and sprinkled on food?
   a. Palladone™.
   b. MS Contin®.
   c. Avinza®.
   d. OxyContin®.

32. Which agents are preferred for the prophylactic management of opioid-induced constipation?
   a. Stimulant laxatives, with a stool softener if desired.
   b. Dietary changes and exercise.
   c. Opioid antagonists.
   d. Opioid-induced constipation should not be treated prophylactically.

33. Opioid-induced respiratory depression is most likely to occur in:
   a. Opioid-naive patients.
   b. Patients with severe pain.
   c. Patients who also experience sedation.
   d. Patients with nonmalignant pain.
34. All of the following strategies may be effective for managing opioid-induced adverse effects except:
   a. Gradual titration of dosages.
   b. Adding a medication to treat the effect.
   c. Adding an adjuvant and decreasing the dosage.
   d. Using an opioid antagonist that only works centrally.

35. One quarter to one third of the starting dose of opioids (calculated based on weight) should be used when treating infants less than 6 months of age because:
   a. Infants this age have immature nervous systems and do not appear to experience pain to the same degree as older children.
   b. Weight-based calculations for opioids are accurate only for infants weighing more than 8 kg.
   c. Infants this age have decreased hepatic and renal function.
   d. All of the above.

36. About 10% of patients in the United States will not obtain analgesia with which opioid because they are poor metabolizers of the drug?
   a. Morphine.
   b. Codeine.
   c. Oxycodone.
   d. Meperidine.

37. Which of the opioids on the following list is most appropriate for use in the elderly?
   a. Meperidine.
   b. Hydromorphone.
   c. Pentazocine.
   d. Propoxyphene.

38. Which of the following classes of drugs are not considered first-line adjuvants for the treatment of neuropathic pain?
   a. AEDs.
   b. TCAs.
   c. SSRIs.
   d. The 5% lidocaine patch.

39. Which of the following statements is false?
   a. Capsaicin depletes substance P from sensory C fibers, which results in analgesia after repeated application.
   b. Antidepressants that inhibit the reuptake of both serotonin and norepinephrine appear more effective for treating pain than those that selectively inhibit the reuptake of serotonin.
   c. Pregabalin has greater efficacy than gabapentin for treating neuropathic pain but appears to require a more prolonged titration period.
   d. SMRs and BTX both appear effective for treating certain pain states that involve muscle spasm or hyperactivity.

40. Which of the following statements is true?
   a. SSRIs are the most effective antidepressants for treating pain.
   b. Local anesthetics should never be administered systemically.
   c. Use of systemic corticosteroids should be limited to short courses of therapy or to patients who are terminally ill.
   d. NMDA antagonists are most useful for managing acute pain states.
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C.E. ASSESSMENT QUESTIONS—ANSWERS

Please circle your answers (one answer per question).

1. a b c d e 11. a b c d e 21. a b c d e 31. a b c d e
2. a b c d e 12. a b c d e 22. a b c d e 32. a b c d e
3. a b c d e 13. a b c d e 23. a b c d e 33. a b c d e
4. a b c d e 14. a b c d e 24. a b c d e 34. a b c d e
5. a b c d e 15. a b c d e 25. a b c d e 35. a b c d e
6. a b c d e 16. a b c d e 26. a b c d e 36. a b c d e
7. a b c d e 17. a b c d e 27. a b c d e 37. a b c d e
8. a b c d e 18. a b c d e 28. a b c d e 38. a b c d e
9. a b c d e 19. a b c d e 29. a b c d e 39. a b c d e
10. a b c d e

C.E. ASSESSMENT FORM

A Pharmacist’s Guide to the Clinical Assessment and Management of Pain

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How long did it take you to read the continuing education program and complete this test?

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My signature certifies that I have independently taken this C.E. Examination:

Follow Up

As part of our ongoing quality-improvement effort, we would like to be able to contact you in the event we conduct a follow-up survey to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

❑ Yes, I am interested in participating in a follow-up survey.  ❑ No, I am not interested in participating in a follow-up survey.

PROGRAM EVALUATION

PLEASE ANSWER EACH QUESTION.

1. Overall quality of the program
   5 4 3 2 1
2. The program was relevant to pharmacy practice
   5 4 3 2 1
3. Value of the content
   5 4 3 2 1

PLEASE ANSWER EACH QUESTION MARKING WHETHER YOU AGREE OR DISAGREE.

4. The program met the stated learning objectives:
   Agree Disagree
   • Discuss the pathophysiology and etiology of different types of pain and their prevalence.
   • Explain the economic, clinical, and humanistic impact of pain.
   • Discuss the appropriate assessment and diagnosis of pain.
   • Describe appropriate pharmacologic and nonpharmacologic strategies for managing various types of pain.
   • Explain how to convert opioid dosages between medications and routes of administration.
   • Discuss pharmacotherapeutic considerations for special patient populations, including patients with renal, hepatic, or other conditions.

5. The program increased my knowledge in the subject area.

6. The program did not promote a particular product or company.

Impact of the Activity

The information presented (check all that apply):

7. Reinforced my current practice/treatment habits  ❑ Will improve my practice/patient outcomes  ❑ Provided new ideas or information I expect to use  ❑ Enhances my current knowledge base
8. Will the information presented cause you to make any changes in your practice?
   ❑ Yes  ❑ No
9. How committed are you to making these changes? (Very committed)  5 4 3 2 1 (Not at all committed)
10. Do you feel future activities on this subject matter are necessary and/or important to your practice?
   ❑ Yes  ❑ No

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