The PainEdu.org Manual:

A POCKET GUIDE TO PAIN MANAGEMENT

A companion to www.PainEdu.org

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Foreword

Pain management continues to become an increasingly important clinical issue and challenge for health care providers. Almost as quickly as new medications are developed, new conditions and theories about appropriate treatment are identified. The burden of unsuccessfully diagnosed and treated pain on society is tremendous, ranging from inability to perform activities of daily living, to poor emotional status and impaired relationships, to tremendous financial impact. Many health care professionals have devoted their careers specifically toward the appropriate assessment and management of pain. These health care providers often act as consultants when their area of expertise is needed.

This manual is intended to serve as a pocket reference for those physicians, health care professionals, and health care students who are not experts in the field, but who are faced with issues surrounding management of patients with pain on a daily basis. We offer this guide as a resource to physicians and health care providers who will inevitably encounter this common and difficult problem that presents in many forms. The current edition has been updated to try to keep up with modalities, approaches, and regulations as they continue to evolve. It should serve as a handy tool to quickly guide the health care provider in the right direction toward the assessment and appropriate treatment of common painful conditions.

Although it would be impossible to cover all conditions and details in a handy reference, we feel confident that this manual, in conjunc-

tion with its companion web site, http://www.PainEDU.org, will become an invaluable part of your quick-reference library for treating the common painful conditions affecting your patients' lives.

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I.

Basic Principles of Pain Management

BASICS OF PAIN TREATMENT

> "We must all die. But that I can save him from days of torture, that is what I feel as my great and ever new privilege. Pain is a more terrible Lord of mankind than even death itself."
>
> —Albert Schweitzer

Pain is a phenomenon that all people encounter at some point in their lives. Both a sensory and an emotional experience, *pain* is defined as being an unpleasant experience associated with actual or potential tissue damage. Pain, in both its acute and chronic manifestations, can commandeer a patient's body and mind. When improperly managed, pain can lead to decreased productivity and diminished quality of life.[1] The consequences of inadequate attention to pain reach into the professional, family, sexual, and avocational realms.

Pain is treatable, however. As the science of pain continues to unravel the mystery of its mechanisms, doctors have an increasingly large arsenal of tools to deploy against pain. There are clinically accepted methods for assessing pain in adult, pediatric, and elderly populations. Each of these measures is calibrated to elicit the most accurate self-report from a patient of a certain age group and level of cognitive ability. In addition, a review of a patient's medical history and a thorough physical and neurologic examination can be useful tools in qualifying and quantifying pain.[2]

Using these measurement tools, a health care provider is empowered to treat pain with pharmacologic, nonpharmacologic, and psychological remedies. Treatment should be tailored to the type of pain, the location of the pain, its duration, and its intensity. Other considerations include, but are not limited to, the patient's medical history and previous reactions to particular drugs. Assessment of the psychological and social consequences of pain is an important part of tailoring treatment. Multimodal treatment strategies are often necessary to achieve success. Any pain treatment needs to be fine-tuned to a patient's particular needs. There is almost invariably a trial-and-error period while the regimen is adjusted. It is also essential that the patient and his or her family understand well the limitations of pain management.

Modern society has high expectations for health care, and it is important to communicate that complete relief from pain is frequently not possible. Special considerations apply in cases of young patients, those who are cognitively impaired, those with psychiatric comorbidities, and patients at the end of life. In managing pain, the emphasis should be on effectively minimizing discomfort and maximizing function while attending to its underlying cause.

When treating pain, regardless of the modalities used, some basic "pearls" that appear in Table 1 below are worth keeping in mind.

Table 1.
Basics of Pain Treatment

Analgesia should be integrated into a comprehensive patient evaluation and management plan.
The emotional and cognitive aspects of pain must be recognized and treated.
There is no reliable way to objectively measure pain.
Pain is most often undertreated, not overtreated.
Pain control must be individualized.
Anticipate rather than react to pain.
Whenever possible, let the patient control his or her own pain.

(continued)

Table 1.
Basics of Pain Treatment (Continued)

Pain control is often best achieved by rational polypharmacy.
Pain control often requires a multidisciplinary, team approach.

Adapted from Ducharme J. Acute pain and pain control: state of the art. *Ann Emerg Med* 2000;35:592–603.

BARRIERS TO THE ASSESSMENT AND MANAGEMENT OF PAIN

Despite the fact that principles and tools exist for assessment and treatment of pain today, barriers exist that may hinder successful outcomes. Improved education about appropriate assessment and treatment of pain will, it is hoped, someday conquer some of these barriers and the myths they promote.

Even though the decade beginning in 2000 was designated as the "Decade of Pain Control and Research" by the U.S. Congress, the health care system still lacks clearly articulated primary care practice standards for pain management. Other than the Joint Commission on Accreditation of Healthcare Organizations' institutional standards, there is a noticeable absence of accountability and competency for adequate assessment and management. The growth of managed care has also led to fragmentation and lack of communication among physicians, leading to less coordination of care. Obviously, financial barriers, such as lack of insurance, may lead to a lower level of care.

Clinician perception of the relative importance of pain and its management can also lead to undertreatment. Some health care professionals do not want to routinely accept the patient's self-report of his or her degree of pain as credible. Fear of regulatory scrutiny may also inhibit efforts to control pain.

The inability of the patient to report symptoms accurately, such as with cognitively impaired patients, may result in poor communication with the health care provider and a decreased likelihood of successfully understanding the patient's needs.

Table 2.
Common Myths about Pain

Children do not feel pain to the same degree as adults.
It is not possible to adequately measure pain in cognitively impaired patients.
Physical manifestations of pain are more important than self-report measurements.
Pain does not exist in the absence of detectable tissue damage.
Pain without an obvious source is usually psychogenic.
The same stimulus produces the same degree of pain in all individuals.
Analgesic therapy should not be started until the cause of pain is established.
Noncancer pain is not as severe as cancer pain.
Knowledgeable patients have a higher incidence of drug diversion.
Use of opioids causes all patients to become addicted to them.
Aggressive pain management is synonymous with prescribing opioids.

These barriers are associated with a number of myths about pain and its treatment.

IMPORTANCE OF TIMELY REFERRAL TO A PAIN SPECIALIST

Many painful conditions may be managed adequately by the primary care clinician. However, referral to a pain specialist or a pain management team may be best for certain cases of chronic, cancer-related, or otherwise complex pain that is debilitating or refractory to treatment.[3]

Important members of the pain management team may include the following:

- Anesthesiologists
- Clergy

- Counselors
- Neurologists
- Nurse specialists
- Physiatrists
- Physical or occupational therapists
- Psychiatrists
- Psychologists
- Social workers

Pain clinics may bring all relevant team members "under one roof." Many pain specialists believe that referrals frequently are made past the so-called "golden hour," when their intervention may be of maximal effectiveness, especially in cases of neuropathic and cancer pain.[4] Referral to a pain specialist ideally should occur before significant disability or loss of function occurs; pain behaviors or the emergence of maladaptive coping strategies may serve as cues for referral.

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II.

The Epidemiology of Pain

DEFINITION OF PAIN

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."

Pain is a ubiquitous phenomenon. As clinicians know, the same set of circumstances can cause significant pain in one patient and little or none in another. The challenge, then, is not only to identify the type and source of pain a patient is experiencing, but also to assess the severity and impact that the painful condition has on the individual patient to ensure optimal treatment. Pain is somewhat of a "black box," in that only the sufferer fully understands the experience. Pain has both subjective and objective components, the proportions of which may be variable but all of which must be treated. Additionally, consideration must be given to the temporal nature of the pain, as treatment strategies for acute pain may differ dramatically from those for chronic pain.

INCIDENCE AND PREVALENCE OF PAIN

Almost everyone experiences pain at some time in his or her life. Pain is the single most common reason for patients to seek medical attention.[1] On average, 15–20% of Americans experience chronic pain each year, approximately 68 million Americans. Americans seek advice from a physician on average 3.1 times per year,[2] and the majority of these contacts are precipitated by complaints of some type of

pain. In the case of back pain, one of the most prevalent forms of chronic pain, age has been found not to be a major influence on its incidence.

Surgery is the single largest cause of acute pain in the United States, with approximately 41.5 million Americans undergoing hospitalization for surgery each year.[2] The majority of patients in the United States report moderate to severe pain postsurgically, even in the face of current treatments and techniques.

As the American population continues to age, there is an increase in the burden of arthritis pain and chronic joint symptoms in people aged 65 or older.[3] In a 1999 poll, a large proportion of respondents indicated some degree of disability secondary to pain, with two out of three elderly individuals responding that pain kept them from participating in activities. Arthritis is the leading cause of disability, with approximately 39 million physician visits and 500,000 hospitalizations per year.[4] Cancer, the second leading cause of death in America,[5] is associated with chronic pain in approximately 67% of patients.[6]

BURDEN OF PAIN ON SOCIETY

Besides the physical, physiologic, and psychosocial effects of pain on individual patients, the burden placed on our society in financial terms is tremendous. In 1998, the National Institutes of Health estimated the financial burden of pain to be as much as $100 billion per year in medical expenses, lost wages, and other costs, including lost productivity. This loss of productivity is often largely invisible to employers because it includes under-performance on the job due to pain, as well as time off the job.[7]

The American Productivity Audit, a survey of 28,902 working adults, found the following in relation to pain-related work productivity[8]:

- 52.7% of the work force surveyed reported having headache, back pain, arthritis, or other musculoskeletal pain in the prior 2 weeks.

- 12.7% of the work force lost productive time in a 2-week period due to pain.
- Headache (5.4%) was the most common pain condition prompting lost productive time, followed by back pain (3.2%), arthritis pain (2%), and other musculoskeletal pain (2%).
- Headache produced, on average, 3.5 hours of lost productive time per week.
- Overall, workers lost an average of 4.6 hours per week of productive time due to a pain condition.
- Lost productive time from common painful conditions was estimated by this study to cost $61.2 billion per year.
- 76.6% of lost productive time was explained by reduced work performance, *not absenteeism*.

PATIENT DESCRIPTIONS OF PAIN

Pain is described by patients experiencing it in words that relate to physical sensations, such as "tingling" or "aching," and in emotional words, such as "horrifying" or "terrifying." To illustrate pain, people often use vivid verbal analogies such as "I feel like someone is stabbing me repeatedly and twisting the knife," or "My head is in a vise that is being squeezed tighter and tighter." Behavioral responses, including grimacing, bracing, or rubbing the affected area, result in nonverbal communication about pain. These behaviors, and the accompanying physiologic signs and symptoms of autonomic activation (e.g., tachycardia, tachypnea), are common in acute pain but are uncommon in chronic pain, even when it is severe. Physicians and health care providers can feel challenged when called on to evaluate and treat painful sensations and the suffering they evoke.

The importance of alleviating the adverse consequences of pain and improving pain treatment globally was recognized by the World Health Organization in 1990. The United States government has officially designated 2000–2010 as the "Decade of Pain Control and

Research." Pain has now earned the official designation as the "fifth vital sign," and patients are encouraged to understand that they have the right to effective assessment and adequate treatment of pain.[9]

Much can be done to improve pain assessment and treatment, as this manual and the accompanying Web site http://www.PainEDU.org demonstrate.

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III.

Pathophysiology of Pain

MECHANISM OF NORMAL PAIN

In the past, it was thought that a sensory input, such as a pinprick, would cause a pain "signal" to be sent directly to the brain via a single nerve. Although not completely understood today, the science of pain reveals a much more complex process that still is continuing to evolve. New receptors, pathways, and hypotheses are being investigated every day. The following is a brief review of basic concepts important to understanding the physiology of pain. For more detailed information on this topic, as well as new developments, the reader is strongly urged to visit http://www.PainEDU.org.

THE PAIN PATHWAY

Four steps occur along the pain pathway: transduction, transmission, modulation, and perception.[1]

Transduction is the process by which afferent nerve endings participate in translating noxious stimuli (e.g., a pinprick) into nociceptive impulses. Silent nociceptors, also involved in transduction, are afferent nerves that do not respond to external stimulation unless inflammatory mediators are present. The peripheral nervous system contains primary sensory afferent neurons that have an important role in pain signaling. The axons of these afferents diverge from the cell body in the dorsal root ganglion near the spinal cord and send a short fiber centrally into the cord and a long fiber down the peripheral nerve into the tissues. Their receptors detect mechanical, thermal,

proprioceptive, and chemical stimuli. There are three types of primary afferents: A beta fibers, A delta fibers, and C-fibers. A beta fibers are myelinated, large-diameter fibers that respond primarily to light touch and moving stimuli, such as vibration. A delta fibers (myelinated, small-diameter fibers) and unmyelinated C-fibers respond to noxious (potentially painful) stimuli. Fibers that respond maximally to noxious stimulation are classified as pain fibers, or *nociceptors*. These are generally A delta fibers and C-fibers. These nociceptors respond to noxious mechanical, thermal, and chemical stimuli.[2]

Noxious stimulation is first carried by the faster A delta fibers and then by the slower C-fibers. Local injury can cause nociceptors to become hypersensitive to noxious stimuli, thereby creating a condition called *sensitization* mediated by algogenic (i.e., pain-generating) substances in the periphery. A sequence of events occurs after local tissue injury, including local vasodilation, edema, and spreading vasodilation (flare), which is known as the *triple response of Lewis*. This is accompanied by *hyperalgesia* (an exaggerated response to painful stimuli) in the injured area (primary hyperalgesia) and hyperalgesia that spreads beyond the injured area (secondary hyperalgesia).[3]

Transmission is the process by which impulses are sent to the dorsal horn of the spinal cord, and then along the sensory tracts to the brain. The primary afferent neurons are active senders and receivers of chemical and electrical signals. Their axons terminate in the dorsal horn of the spinal cord, where they have connections with many spinal neurons. In turn, spinal neurons have inputs from many primary afferents. These spinal neurons project axons to the contralateral thalamus, which in turn projects to the somatosensory pathway, frontal cortex, and other areas. The somatosensory cortex is thought to be involved in the sensory aspects of pain, such as the intensity and quality of pain, whereas the frontal cortex and limbic system are thought to be involved with the emotional responses to it.

The major ascending tract is the spinothalamic tract (STT). Cell bodies of the STT are located primarily in lamina V, but also in laminae I, VII, and VIII. These neurons have axons that cross to the opposite side of the spinal cord and enter its anterolateral quadrant.

The STT divides in two different pathways as it approaches the thalamus. The neospinothalamic tract, or lateral STT, is the tract that subserves the sensory/discriminative aspects of pain perception. It synapses on the lateral thalamus and projects to the somatosensory cortex. The medial STT, or paleospinothalamic tract, synapses in the brain stem reticular formation, the medial thalamus, periaqueductal gray matter, and the hypothalamus and has subsequent projections to the cortex and limbic system. This tract subserves the affective/motivational aspects of pain perception.[3]

Modulation is the process of dampening or amplifying these pain-related neural signals. Modulation takes place primarily in the dorsal horn of the spinal cord, but also elsewhere, with input from ascending and descending pathways. Rich arrays of opioid receptors (mu, kappa, and delta) are present in the dorsal horn. In addition to an ascending tract, the nociceptive system contains descending pathways that send neurons from the frontal cortex and hypothalamus to the midbrain and medulla. These neurons inhibit nociceptive neurons and interneurons in the ascending pathway.[4] Important centers of this descending antinociceptive modulation system are the periventricular and periaqueductal gray matter, the dorsolateral pons, the nucleus raphe magnus, and the rostroventral medulla. Descending pathways project axons to laminae I, II, and V in the spinal cord. In addition to endogenous opioids, the biogenic amines (serotonin and norepinephrine) are neurotransmitters involved in this process. A variety of modalities can activate the descending antinociceptive pathways, including systemic or neuraxial injection of opioids, electric stimulation, stress, suggestion, and pain.[3]

The *gate control theory* is a popular model of pain modulation proposed by Melzack and Wall in 1965 and later revised by Melzack and Casey in 1968. These investigators proposed the existence of an endogenous ability to reduce or increase the degree of perceived pain through modulation of incoming impulses at a gate located in the dorsal horn of the spinal cord. The gate acts on signals from the ascending and descending systems and weighs all of the inputs. The integration of these inputs from sensory neurons, the segmental spi-

nal cord level, and the brain determines whether the gate will be opened or closed, either increasing or decreasing the intensity of the ascending pain signal. The importance of psychological variables in the perception of pain, including motivation to escape pain, and the role of thoughts, emotions, and stress reactions in increasing or decreasing painful sensations is evident in the gate control theory. An example of this is when patients report more pain at night when they are isolated and less distracted from their pain than they might be during the day. The proposed gate can be opened or closed by pharmacologic manipulation, transduction, transmission and modulation, and psychological intervention.

Perception refers to the subjective experience of pain that results from the interaction of transduction, transmission, modulation, and the psychological aspects of the individual.

Table 3.
Normal Pain Pathway at a Glance

Transduction	Transmission	Modulation	Perception
The process by which afferent nerve endings participate in translating noxious stimuli (e.g., a pinprick) into nociceptive impulses	The process by which impulses are sent to the dorsal horn of the spinal cord and then along the sensory tracts to the brain	The process of dampening or amplifying pain-related neural signals, primarily in the dorsal horn of the spinal cord, but also elsewhere, with input from ascending and descending pathways	The subjective experience of feeling pain that results from the interaction of transduction, transmission, modulation, and psychological aspects of the individual

DEFINITION OF ABNORMAL PAIN

Pain associated with the functioning of the unaltered nociceptive system, such as stepping on a thumbtack or touching a hot stove, is referred to as *normal pain* or *nociceptive pain*. Pain that occurs in the context of a nociceptive system that has been altered by tissue damage or other processes may be referred to as *abnormal pain*. There are a number of different ways of classifying abnormal pain, with no universally accepted approach. Following is a classification system that appears to represent emerging consensus.

Inflammatory pain is the sensation that results from injury to a somatic tissue (e.g., skin, muscle, bone), which is invariably followed by an inflammatory reaction. For example, inflammatory pain is felt as the result of an acute injury or infection. The pain produced consequent to tissue inflammation results from a number of different processes. The release in injured tissue of so-called algogenic substances such as bradykinin and serotonin results in "sensitization" of the peripheral nociceptors, resulting in a lower threshold for firing and an increased frequency of firing compared with their resting state. Sensitization of nociceptive afferents means that these neurons now respond to non-noxious stimuli, such as a light touch or contact with clothing. So-called silent nociceptors may also be recruited; these are nociceptive nerve fibers that normally are silent, but in the setting of inflammation generate "pain" signals. After tissue healing, the pain generally resolves. However, in states of ongoing inflammation, such as rheumatoid arthritis or cancer, pain persists. In cases where inflammation may resolve but leave permanent anatomic alterations, such as the joint damage produced by osteoarthritis, chronic pain may result even though inflammation disappears or becomes inconspicuous.

What mechanisms lead inflammatory pain to become chronic or severe? One proposed mechanism is *central sensitization*, which refers to the process by which, as a consequence of excessive nociceptive nerve signals bombarding the central nervous system from the periphery, long-term changes occur in the central nervous sys-

tem that result in persistent amplification of pain signals. One experimental paradigm resulting in central sensitization is known as *wind-up*; there are also other pathways to central sensitization. Central sensitization is one proposed mechanism by which in the context of inflammation or nerve injury (see below) normally innocuous stimuli produce pain, such as is seen in many cases of postherpetic neuralgia.[2] The phenomenon of normally innocuous stimuli (such as light touch) producing pain is called *allodynia*.

Central sensitization may also cause an exaggerated response to normally painful stimuli; this is called *hyperalgesia*. *Primary hyperalgesia* occurs at the site of injury and is characterized by a lower pain threshold, spontaneous pain, and increased sensitivity. It usually features thermal and mechanical hypersensitivity.[3] *Secondary hyperalgesia* refers to hyperalgesia occurring outside the area originally injured and is thought usually to be a consequence of central sensitization. The significance of the distinction is that to effectively treat chronic pain, hypersensitivity must be addressed during the clinical assessment of patients. Therapy that targets the mechanisms of hypersensitivity, if present, rather than mechanisms of nociception, must be used to try to alleviate symptoms.[4]

Neuropathic pain is defined as pain due to damaged or dysfunctional nerves. The pathophysiology of neuropathic pain can have both peripheral and central mechanisms. There have been multiple proposed mechanisms for both peripheral and central components to the pathophysiology of neuropathic pain; it is doubtful that a single mechanism can account for all cases. Damaged primary afferents may generate signals at ectopic or abnormal locations and their excitability increases after mechanical stimulation. In addition, nerves that are cut off from input from the periphery, as in the case of amputation, may become hyperactive. Changes in the dorsal horn after nerve injury include reorganization, modulation in sensory input, enlargement of the second-order neuron's receptive field, alteration in opioid receptivity, abnormal ingrowth of sympathetic nerve terminals, and abnormal temporal summation.[5] Thus,

central nervous system changes, as well as peripheral nerve changes, may generate neuropathic pain.

Woolf and Mannion categorize peripheral neuropathic pain as either spontaneous (*stimulus-independent*) or hypersensitive (*stimulus-evoked*) because of increased sensitivity after damage to sensory neurons.[6]

Dysfunctional pain refers to a pain syndrome in which patients experience pain and abnormal sensitivity not associated with noxious stimulus, tissue damage, inflammation, or identifiable lesion to the nervous system. The conditions encompassed by dysfunctional pain may include fibromyalgia, tension-type headaches, migraines, and even irritable bowel syndrome. Individuals with these syndromes share a number of common characteristics, including hypervigilance to sensory stimuli, exaggerated experience of a diverse array of sensory stimuli (e.g., pain, but also sound, light, etc.), high prevalence of associated conditions (e.g., the high prevalence of irritable bowel syndrome in patients with fibromyalgia), and in some cases abnormal biomarkers (e.g., opioid peptides in spinal fluid).

There are many other ways of describing pain and terms that support them. An important term is *referred pain*, the perception of pain in a body part in which it did not originate (e.g., feeling pain from the diaphragm near the shoulder). The mechanism of referred pain is thought to be convergence of primary afferents from different locations (e.g., shoulder and diaphragm) onto the same spinal cord neurons. Because spinal neurons subserve both deep structures and skin, mislocation of sensations is possible. Classification of pain into different types and mechanisms is more than just academic interest. Data continue to emerge indicating that different types of pain respond to different types of treatment, so that accurate classification of the type of pain can support accurate selection of treatment options for the individual patient.

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IV.

Pain Assessment

DEFINITIONS

Regardless of whether or not pain is nociceptive, neuropathic, or idiopathic, it is usually broadly categorized as either *acute* or *chronic*. Pain is also categorized based on other characteristics, such as its intensity, location, quality, and factors that alleviate it or worsen it.

Some simple distinguishing characteristics of acute and chronic pain include the following:

- Acute pain
  - Generally sudden onset, certainly recent onset
  - Obvious identifiable cause
    - Injury
    - Disease
    - Iatrogenic (e.g., surgery)
  - Short duration (less than 1 month)
  - Intensity generally variable and indicative of severity of condition
  - Characteristic behavior, such as rubbing, moaning, crying
- Chronic pain
  - Persistent (3 months duration or longer), often undetermined onset
  - Usually the result of some chronic disease or condition
  - May have no obvious cause
  - Prolonged functional impairment
    - Physical
    - Psychological

- May or may not be associated with characteristic behavior such as insomnia, anorexia, irritability, and even depression
- Often more difficult to manage than acute pain

Basic Terminology

Acute pain is pain that is the result of an injury or illness that is time-limited and of recent onset. Low back pain after an injury, acute headache, and postoperative pain are examples of acute pain. Acute pain is generally thought to have the biologic function of alerting the individual to harm and preparing for the "fight-or-flight" response to danger. Diagnosing and treating the underlying cause of pain, in addition to treating the symptomatic pain, are the critical elements of pain management. *Subacute pain* is pain that usually lasts up to 3 months.

Baseline pain is pain that is generally constant in nature and lasts at least half of the day.

Breakthrough pain is pain that increases over baseline pain to a significantly higher degree of intensity. *Incident pain* is a type of breakthrough pain that increases with activity or movement.

Chronic pain is pain that persists and does not resolve spontaneously. Chronic pain has usually been defined arbitrarily as pain that persists for 3–6 months or beyond the period of time that healing could be expected to have occurred.[1] Ongoing or progressive tissue damage may be present in some types of chronic pain, including progressive neuropathic pain and rheumatologic conditions. In other cases, chronic pain may be present when tissue damage is stable or undetectable.

Nociception is the activity in peripheral pain pathways that transmits or processes information about noxious events usually associated with tissue damage. Pain is the perception of nociception, which occurs in the brain. In some conditions, such as diabetic peripheral neuropathy, nociception due to tissue damage may occur, but the patient may not perceive, or feel, it. Conversely, the patient may perceive severe pain with no demonstrable evidence of tissue damage (e.g., trigeminal neuralgia).

Pain Categorized by Source and Related Nociceptor

Cutaneous pain is caused by injury to skin or superficial tissues. Cutaneous nociceptors terminate just below the skin and have a high concentration of nerve endings, producing well-localized pain.

Somatic pain originates from somatic nociceptors, located in structures such as ligaments, bones, blood vessels. The low concentration of nerve endings results in a dull, poorly localized pain sensation that is usually of longer duration than cutaneous pain.

Visceral pain originates from organ-level nociceptors located within the organs themselves or visceral cavities. Visceral nociceptors exist in even lower concentrations than somatic or cutaneous nociceptors, resulting in even more elusive qualities with respect to localization. The quality of visceral pain is typically more of a diffuse aching pain of longer duration.

Assessment

Careful and accurate assessment of pain is critical for successful diagnosis and treatment. Some important first steps include identifying some key points with respect to the patient's pain:

- The description of painful symptoms (e.g., burning, throbbing)
- The location of the pain
- The temporal nature of the pain
  - Acute versus chronic
  - Time of occurrence and duration
- The severity of the pain
  - Impact on activities of daily living
  - Psychological impact
  - Social impact
- Exacerbating and alleviating factors
- Steps taken before managing the pain
  - Reduction in activity
  - Medication use before visit

Pain assessment is not a one-time phenomenon. According to the Joint Commission on Accreditation of Healthcare Organizations Stan-

dards for 2001,[1] pain is now considered to be the fifth vital sign and should be assessed initially and reassessed on a scheduled and regular basis. The National Comprehensive Cancer Network guidelines of 2000 indicate that severe cancer pain should be assessed every 15 minutes for rapid titration of short-acting opioids and at least every 24 hours after administration of oral opioids. Patients can be informed of the regularity of pain assessment and informed that a score above a predetermined level will be addressed.

To begin an assessment, all patients should be asked about the presence of current pain or of pain over the past several months. Clinicians often ask, "How can I know how much pain my patient is feeling?" Unfortunately, there are no objective tests that can indicate the precise quality and intensity of pain and tease out the patient's affective and behavioral reactions to it. Because of the multiple dimensions of pain, it is considered to be a purely subjective experience. There are, however, standardized measures and clinical questions that can be used to assess pain and associated symptoms, such as sleep disturbance and functional status. These measures rely primarily on the patient's self-report, which, despite its limitations, remains the single most reliable indicator of the existence and intensity of pain. Techniques to assess pain when self-report is unavailable or unreliable are introduced in Chapter VII. In this section, several commonly used measures of pain intensity are reviewed, as are clinical interview questions that form part of the pain assessment. Important points of assessment in the physical examination and thorough diagnostic testing are also reviewed.

PATIENT HISTORY

Much of the information the clinician gleans about the patient's pain complaint is gained in a thorough history and physical examination. The following sample questions should be included as part of a thorough clinical history evaluation:

- What is the location, quality, and frequency of pain?

In addition to pointing to the location of the pain and a verbal description, the patient can draw the location of pain on a body diagram. Primary and secondary sites should be elicited because patients often experience more than one location of pain. In addition, the patient can be asked to assign the percentages of pain in each area relative to the overall pain he or she experiences. Diagnostic information can be obtained by asking about the quality of pain. For example, neuropathic pain is often described as "tingling, burning, shooting," whereas visceral pain is often described as "dull, aching, or squeezing." The frequency of pain can be constant, intermittent, or cyclic, with exacerbations that occur over and above a consistent level of pain. The presence and timing of exacerbations may indicate the need for increased analgesic medication or nonpharmacologic interventions.

- What are the variations and patterns of pain? What factors alleviate or worsen pain?

Patterns of pain can be helpful in diagnosis and treatment. Patients with consistent patterns of morning pain can have their medication regimen adjusted to help them accomplish morning routines. The temporal pattern of pain—that is, whether it is constant or intermittent, sudden or gradual—is one of the most important elements in the medical history that leads to diagnosis. Provocative factors, such as bending forward or backward, may also be helpful in determining the differential diagnosis.

- When was the onset of pain? What is the history of pain management interventions? How did each of these interventions work?

The onset of pain, both in terms of the duration of pain and the manner in which the pain occurred (acute, accident, insidious), has implications for treatment and may hold meaning for the patient. For example, an insidious onset of pain with an unexplained etiology may have different implications in terms of seeking treatment and coping with pain. Patients should be asked about their use of pharmacologic, nonpharmacologic, and procedural interventions for pain. The patient may have used alternative or complementary medical approaches, such as the use of herbal preparations, acu-

puncture, or magnets. The relief experienced from each of these interventions can be measured by using a visual analogue scale (VAS) or by asking the patient to assign a percentage value of relief (e.g., 50% pain relief from the use of nonsteroidal antiinflammatory drugs) for each treatment.

- What are your physical limitations due to pain?

Patients are generally quick to describe their functional limitations due to pain. Walking, performing domestic chores, or continuing to work in their occupation may all be affected. Individuals in acute pain may be unable to turn over, cough, or breathe deeply secondary to their pain. Special attention should be paid to the ways patients compensate for their inability to perform physical tasks, such as walking. Compensation with another limb (e.g., performing all duties with one hand) can lead to overuse syndromes and/or more serious problems in previously unaffected areas.

- What are your expectations of treatment?

Patients today have high expectations for treatment. Although the probability that these expectations can be met in an acute, postoperative setting is high, the probability decreases for chronic pain conditions. The urgency of treatment and the expectations for it may be based on inaccurate assumptions or beliefs, such as that pain signifies ongoing damage or a return of a cancerous tumor. Patient education about the underlying cause of the pain and the effectiveness of medications, interventional procedures, and nonpharmacologic treatments should be explained carefully and honestly in lay language. Setting appropriate expectations of treatment can itself be of therapeutic benefit.

PHYSICAL EXAMINATION FOR PAIN

The physical examination for patients with pain should include a general physical, neurologic, musculoskeletal, and mental status of a

patient and is likely to be a more complex process than that of other medical patients.[2] In addition, the examination should involve an assessment of the patient's functional abilities. A careful examination of the site of the patient's pain, including anatomic sites of commonly referred pain, should also be performed. The general appearance of the patient, including attributes of the skin, posture, and demeanor, are important aspects of the general physical examination.

Musculoskeletal Examination

The musculoskeletal examination includes an overall examination and focused palpation or manipulation at the site of pain. The examination needs to be tailored to the pain complaint. Muscle systems in the neck, upper extremities, trunk, and lower extremities, should be tested.[2] Deep or superficial muscle tenderness should be noted. The quality of the patient's response to palpation may be considered in the assessment. Vocalizations or a display of pain behavior may be part of the patient's cultural and/or ethnic background and can be of importance when a more stoic individual displays pain behavior in response to palpation.[2] Range of motion, including flexion, extension, side bending, rotating, and straight-leg raises, should be performed when relevant to ascertain whether pain is experienced on movement and to note the presence of functional restrictions. The degree to which these actions are performed and whether pain is incurred during each of these exercises should be recorded.

Neurologic Examination

A tailored neurologic examination is a key component of the physical examination for pain. The screening neurologic examination should include standard elements, with testing of the cranial nerves II–XII. Motor and sensory functioning in the limbs and an evaluation of rectal and urinary sphincter function have been recommended.[3] Sensory deficits are tested by sensitivity to light touch, pinprick, and mechanical and thermal stimuli. Light touch, pressure, or the application of

hot and cold stimuli can cause *allodynia*—that is, the presence of pain from a stimulus that is not normally painful. Hyperalgesia, or extreme pain from stimuli that normally do cause pain, can be tested by single and multiple pinpricks and is evidence of pathology. A motor examination should test for motor weakness, ataxia, apraxia, and decreased endurance.[4] Reflexes should be normal and symmetric. In addition, pathologic reflexive signs, such as those of Babinski, Oppenheim, Gordon, Chaddock, Schaeferand, and Hoffman, should be tested when relevant.

DIAGNOSTIC TESTING

Diagnostic testing can be useful for some pain conditions and may not be useful in other types of pain conditions. Therefore, familiarity with general principles of diagnostic testing is important when assessing patients with pain.

Imaging Studies

Imaging studies show anatomy, not pain. Thus, there may be false-positives where "abnormalities" are revealed that are unrelated to the patient's pain or false-negatives where the anatomy is "normal" yet pain continues. Computed tomography myelogram, magnetic resonance imaging, ultrasound, and radionuclide examinations are used in patients with pain to confirm or rule out a diagnosis based on the patient's report and the physician's assessment. In the presence of certain signs and symptoms, such as an extremely severe headache or a history of malignancy, imaging can be critical to diagnosis and treatment. Imaging is appropriate for potentially serious spinal conditions, including spinal tumor, fracture, and cauda equina syndrome. Imaging studies are necessary for chronic pain conditions (e.g., unremitting cervical or back pain) for which surgery is being considered. However, imaging plays a limited role in some chronic pain conditions. Because suspected pathologic condi-

tions, such as herniated or bulging disks and nerve root scarring, are frequently found in asymptomatic individuals, the need for imaging studies, and interpretation of results, must be carefully considered, lest they result in inappropriate interventions for irrelevant pathology or in distraction from the real cause of the pain.

Neurophysiology Studies

Electromyography and nerve conduction studies are electrodiagnostic procedures that evaluate action potentials and conduction along peripheral sensory and motor nerves. They are used to suggest the presence or absence of nerve entrapment, radiculopathy, trauma, and systemic neurologic disease.[5] These tests can provide useful information in the evaluation of the cause and extent of peripheral nervous system disease, but they are often unnecessary in the diagnosis of neuropathic pain conditions. Because they measure the functioning of large nerve fibers, they are not useful in diagnosing many neuropathic conditions that result from small-fiber damage or dysfunction.[4] Quantitative sensory testing measures the function of large and small nerve fibers in addition to pain thresholds. The technique is currently used for researching the mechanisms of neuropathic pain and is generally not needed for diagnosis and treatment. Analogous to the case of imaging, electromyography/nerve conduction studies show nerve damage, not pain; thus, electromyography/nerve conduction studies may be abnormal but unrelated to the pain, or normal in the presence of pain.

MEASURING PAIN INTENSITY

Knowledge of the patient's current pain intensity is important, as are pain intensity levels over time. Questions about pain intensity generally include a time line (week, month), a parameter (average, least, most), and a rating of pain. Asking about the least and most pain that the patient has experienced over some period of time can establish whether a range of pain exists.

Unidimensional Scales

Two common assessment instruments that can be used to measure pain intensity are the visual analogue scale and the numerical rating scale.

Visual Analogue Scale

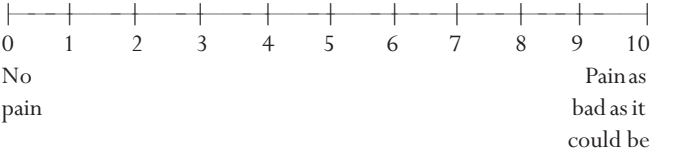
The VAS is a 10-cm line with anchors at both ends. Common anchors are "no pain" and "worst pain." Patients are asked to draw a vertical line through the horizontal line to indicate their pain intensity. The distance from "no pain" to the point at which the patient's line intersects the horizontal line is measured in millimeters, yielding a number between 0 and 100. Research has shown the sensitivity, validity, and reliability of the VAS scale.[6] An example (not to scale) is shown below:

What is the intensity of your pain right now?

Numerical Rating Scale

The numerical rating scale (NRS), sometimes referred to as a *verbal rating scale* (VRS), is an 11-point scale on which patients rate the intensity of their pain by choosing a number from 0 (no pain) to 10 (pain as bad as it could be). This rating scale is commonly used and easy to understand. The scale can be administered visually or verbally, including over the telephone, which can be useful during the dosage titration process.

What is the intensity of your pain right now?

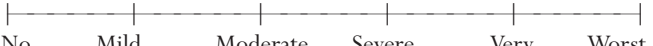


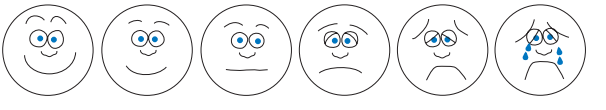
Some investigators prefer the VAS because of certain theoretical psychometric advantages. Others prefer the NRS because fewer patients fail to understand its usage, it is easier to score, and for practical purposes, the psychometric properties work well. A recent survey of 85 chronic pain patients was performed using both the VAS and verbal rating scale.[7] The results of this one survey concluded that comparatively, "the [verbal rating scale] is a simple instrument that can save time and compares favorably to the VAS." Some suggestions for increasing the ease with which patients use the numerical rating scale have been proposed[8] and are also useful in explaining the VAS. The pain scale (e.g., the NRS, VAS) should be explained each time it is administered, and patients should be taught how to use the scale. Patients can be taught that a "10" rating means the worst possible pain. This orientation can reduce the exclusive use of the higher end of the scale and increase the practical application of the measurement. Additional aids can be used to ensure that the patients with hearing or visual difficulties can use the measure with relatively little difficulty. In addition, a quiet place should be provided for the completion of this instrument, and the patient should be allowed to ask questions.[8]

Categorical Scales

Below are two examples of verbal categorical pain scales that provide a simple means for patients to rate their pain intensity using verbal or visual descriptions of their pain.

Simple Descriptive Pain Intensity Scale





	0	1	2	3	4	5
	NO HURT	HURTS LITTLE BIT	HURTS LITTLE MORE	HURTS EVEN MORE	HURTS WHOLE LOT	HURTS WORST
Alternate coding	0	2	4	6	8	10

Figure 1.
Wong-Baker FACES Pain Rating Scale. (Adapted from Hockenberry MJ, Wilson D, Winkelstein ML. *Wong's Essentials of Pediatric Nursing [7th ed].* St. Louis: Mosby, 2005:1259. Used with permission. Copyright, Mosby.)

These unidimensional and categorical pain rating scales remain useful screening tests that frequently should be supplemented by a more detailed assessment.

Multidimensional Tools

Multidimensional pain assessment tools provide information about the pain's characteristics and impact on daily life. The following are three examples of commonly used multidimensional tools for pain assessment in use today.

Initial Pain Assessment Tool

The Initial Pain Assessment Tool was developed for the initial patient pain evaluation. This tool includes a diagram of different body locations so that the patient can mark the areas that correspond to the location of his or her pain. In addition, the following topics are covered in the evaluation:

- Intensity of pain
- Quality of pain (in the patient's own words)
- Onset
- Duration
- Variations

- Presence of rhythmic nature
- Manner of expression of pain
- What, if anything, relieves the pain
- What causes or increases the pain
- What impact the pain has on the patient
  - Accompanying symptoms
  - Sleep
  - Appetite
  - Physical activity
  - Interpersonal relationships
  - Emotional state
  - Ability to concentrate
- Any other pertinent points
- Care plan

Brief Pain Inventory

The Brief Pain Inventory is easy to use and helps to quantify pain intensity and interference with a patient's life. Patients rate their pain severity at its worst, least, and average in the last week and at the time of assessment ("right now").

Brief pain inventory items include the following:

- A diagram of a front and back view of a human figure to identify the location of pain
- A rating of the amount of relief the patient feels that the current pain treatments (if any) provide
- A rating of the duration of the patient's pain relief after taking prescribed pain medications
- An assessment of the patient's attribution of pain to the disease, the treatment of the disease, or conditions unrelated to the disease

Patients also rate their level of pain interference in the following seven contexts from 0 ("does not interfere") to 10 ("completely interferes"):

- Work
- Activity
- Mood
- Enjoyment
- Sleep
- Walking
- Relationships

McGill Pain Questionnaire

The McGill Pain Questionnaire is one of the most extensively used pain scales. The questionnaire consists primarily of three major classes of word descriptors—sensory, affective, and evaluative—that are used by patients to specify their subjective pain experience. It also contains an intensity scale and other items to determine the properties of the pain experience.

The questionnaire was designed to provide quantitative measures of clinical pain that can be treated statistically. The three major measures are the following:

1. The pain rating index, based on two types of numerical values that can be assigned to each word descriptor
2. The number of words chosen
3. The present pain intensity based on a 1–5 intensity scale

Memorial Pain Assessment Card

The Memorial Pain Assessment Card[9] was developed as a rapid multidimensional tool in cancer patients that uses three separate VASs to assess pain, pain relief, and mood. This tool includes a set of adjectives for pain intensity as well. The major advantage of this tool is that it takes very little time to administer; the results also correlate with other, more time-consuming evaluators of pain and mood. The convenience of this card is that it can be carried easily in the clinician's pocket and conveniently presented to the patient one scale at a time.

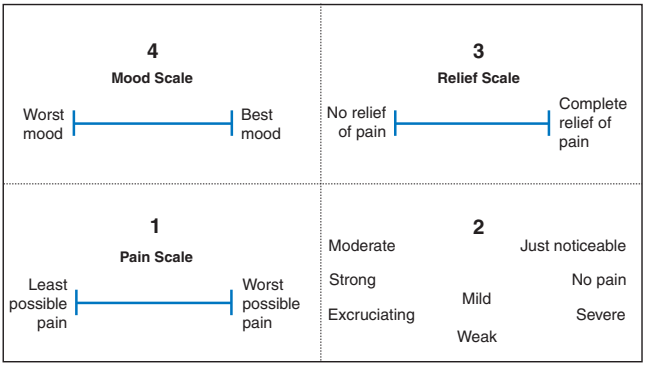


Figure 2.
Memorial pain assessment card.

PSYCHOSOCIAL EVALUATION

Pain affects the patient in many ways psychologically and socially. An overall gestalt of the most salient emotional aspects of pain can be elicited by posing a general question about the patient's well-being, such as, "How is the pain affecting your life?" or "How are you coping with your pain and its effect on your life?" Following are some of the more common areas where patients' concerns may lie.

Emotional Reactions

A variety of emotional reactions can be elicited by persistent pain. Identifying negative emotional content and assessing patients' ability to cope with these emotions are critical to improving their functioning. Asking patients, "What's your mood generally like?" may elicit some of the following:

- Anger: often expressed as frustration, irritability, disgust
- Grief: sadness, blue, loss, "I'm not me"
- Depression: anhedonia, anergia, loss of interest
- Anxiety: nervous, restless, push to be "fixed"

Patients may experience negative emotions about the following:

- Their circumstances (an injury or accident)
- Their diagnosis (cancer, chronic pain)
- An inability to perform tasks previously performed with ease
- Not being able to "handle" pain
- Treatment providers
- Insurance coverage
- The inability to return to previous job
- A terminal illness

Suicidal ideation is relatively common in patients with chronic pain conditions and should be assessed for in every patient and addressed immediately. The risk of death by suicide is estimated to be at least double for patients with chronic pain compared with controls.[10]

Warning Signs for Referral to a Psychologist, Psychiatrist, or Mental Health Professional

- Suicidal ideation with or without intent or plan
- Anergia (i.e., lack of energy)
- Persistent anhedonia (i.e., lack of pleasure)
- Loss of appetite
- Sleep disturbance
- Anxiety or panic
- Prolonged difficulty accepting the condition
- Angry outbursts toward self or others

Cognitions, Coping, and Beliefs about Pain

Cognitions, or thoughts the patient has, exert powerful effects on emotional reactions, behavioral responses, and interpretations of pain. Beliefs are a foundation for cognitions. For example, the belief that the etiology of pain can be "fixed" or "cured" affects expecta-

tions of and satisfaction with treatment. Some maladaptive beliefs and cognitions according to research include the following:

- *Catastrophizing: a cognitive and emotional process that involves magnification of pain-related stimuli, feelings of helplessness, and a negative orientation to pain and life circumstances.*[11] Examples of catastrophic statements include "I can't handle this pain," "There is nothing I can do about my pain," and "My pain is uncontrollable." The effect of catastrophizing should not be underestimated. Catastrophizing is associated with depression, decreases in physical functioning, increased pain,[12] risk of death by suicide,[10] and interpersonal distress.[13] Recent studies suggest that catastrophizing may be related to cortical responses to pain[14] and, potentially, inflammatory disease activity.[11] Catastrophizing predicts poor outcomes for patients with chronic pain and should be treated with cognitive-behavioral therapy.
- *Belief that persistent pain signals ongoing tissue damage.* This belief results in fear of movement, physical activity, and the future. Educating the patient that hurt does not equal harm and appropriate physical activity should continue may be needed.
- *Belief that if a cause of pain can be found, a treatment will fix it.* Patients are generally socialized to believe that medicine has a cure for their problems. Many believe that once a cause of the pain can be found, a treatment that results in a cure is likely (e.g., removing a problematic disk always resolves pain). For many, accepting that chronic pain can be managed but not necessarily cured is a gradual process. Encouragement to continue to be engaged in life as pain is being managed and not wait for a "cure" is often necessary.
- *Belief that pain is a signal to stop activities and movement.* Some patients believe that pain means that they should rest and be inactive. Social activities may be curtailed or stopped because they feel pain. Although patients may not be able to perform the same physical activities as before, they should be encouraged to do as much as possible because physical inactivity increases pain.[15]

Constructive coping styles, such as using coping self-statements and increasing behavioral activities, have been shown to be more effective ways to manage chronic pain[16] than passive coping strategies (e.g., resting).

The patient should be asked how he or she generally copes with pain, both cognitively (e.g., "What do you tell yourself when you are having a pain flare up?") and behaviorally (e.g., "What do you do when you are having a pain flare-up?"). Increases in drug, tobacco, and alcohol use or taking more medication than is prescribed can be other maladaptive ways of coping with pain that can lead to an exacerbation of the difficulties in the patient's life.

Behavioral Reactions

Verbal and nonverbal expressions of pain include a range of behaviors, such as the following:

- Grimacing
- Rubbing the affected body part
- Guarding or restricting movement
- Sighing
- Groaning, wailing
- Taking medications
- Resting

These behaviors are overt and are called *pain behaviors*. They can be used to do the following:

- Communicate distress
- Cope with pain
- Elicit solicitous behavior from others
- Express pain in a culturally learned or valued manner
- Express pain when verbal skills are absent or impaired

The frequency with which pain behaviors are displayed, as well as an evaluation of the environmental responses received, may be helpful in assessing whether these expressions are adaptive or maladaptive in a particular circumstance. The expression of pain behav-

iors may be critical when an individual is unable to express pain verbally (e.g., children, cognitively impaired individuals).

Some behaviors (e.g., resting, taking medication) are problematic when used exclusively as a pain-coping strategy. Sleep disturbance, including insomnia and middle-of-the-night awakening, initially related to painful exacerbations, can become conditioned behavioral responses over time.

Family Functioning and Responses to Pain

The family system is affected when one person becomes unable to function in the expected manner. The responses of family members have been categorized in three ways[17]:

1. Solicitous (e.g., providing assistance or special attention to the patient)
2. Punishing (e.g., becoming angry when pain is expressed)
3. Distracting (e.g., encouraging the patient to distract from the pain)

Research has shown that overly solicitous behaviors or punitive responses from family members or friends are generally not helpful. Research with patients with cancer pain and their families reveals that misconceptions about cancer and pain control on the part of the family have an adverse effect on patient care and outcome.[18]

Those with pain may not be able to fulfill role behavior they perceive as important to their definition of themselves as fathers, mothers, or members of a family or friendship network. For example, a father may not be able to participate in athletic activities with his children and may define this ability as an important part of his role as a father. Families may need assistance changing roles and learning to interact with a person with chronic pain on a long-term basis.

Social and Occupational Functioning

The nature and extent of some chronic pain conditions impact the ability to work and interact in social settings. The stress that accom-

panies the loss of work involves the loss of a sense of purpose, as well as loss of financial compensation.

Work-related injuries are particularly difficult for workers who believed they were valued employees who became relegated to a "disabled" status after their injury. The process of workers' compensation is complex and sometimes adversarial. Patients might experience the following:

- Be required to participate in independent medical examinations by nontreating physicians to review the appropriateness of treatment
- Be followed by private investigators who routinely investigate claims for fraud
- Be disregarded by coworkers because the pain cannot be seen and the patient "looks good"
- Be sent back to work prematurely
- Be asked to interview for other positions
- Be treated differently by physicians because of their litigation status
- Be denied treatment the treating physician has recommended
- Be financially stressed because of the loss of full-time salary or wages

Patients sometimes feel disbelieved and may feel accused of faking an injury or illness for the purpose of personal gain (e.g., obtaining time off) or malingering. Of course, this process is made difficult for physicians and patients because a few patients are malingerers. Malingering involves the intentional production of false or grossly exaggerated physical or psychological symptoms for the purpose of tangible external incentives, such as obtaining financial compensation, evading criminal prosecution, avoiding work or military duty, and obtaining drugs.[19]

The presence of workers' compensation or litigation status does not mean the patient does not want to improve and return to work or is demonstrating malingering, although these factors may complicate recovery. Evaluating the obstacles to recovery or rehabilitation (e.g., the patient does not want to return to a former job or

employer) and addressing these obstacles during treatment (e.g., with vocational counseling) are important components of treating patients with chronic pain.

Psychiatric Disorders and Pain

Painful conditions, like all medical conditions, affect patients with psychiatric disorders. Selected psychiatric disorders are found in greater prevalence in medical settings and in persons with chronic illnesses. Persons with chronic pain are most often diagnosed with depression, anxiety, and substance-use disorders.[20] Consider the following statistics for individuals meeting criteria for major depressive disorder:

- 2% of people in the community[21]
- 5–9% in ambulatory care[21]
- 15–20% of medical inpatients[21]
- 0–58% of persons with cancer[22]
- 43% with nondisabling pain and depression in primary care[23]
- 66% with disabling pain and depression in primary care[23]

A Word about Somatization Disorder

Some psychiatric disorders have as a primary characteristic the existence of abnormal illness behavior and are therefore more likely to present in medical settings. For example, somatization disorder is characterized by the following:

- A pattern of multiple physical complaints
- Significant social and occupational impairment
- Symptoms that occur before age 30
- Symptoms that last for a period of years
- Pervasive complaints unaccounted for by a general medical condition, including the following:
  - Four different pain symptoms
  - Two gastrointestinal symptoms
  - One sexual symptom and
  - One pseudoneurologic symptom[19]

Although the presence of unexplained somatic symptoms is common, somatization disorder is rare.[21]

The diagnosis of undifferentiated somatoform disorder is less restrictive than somatization disorder, requiring one or more physical complaints that cannot be explained by a general medical condition and that cause significant social or occupational distress. Care should be taken before labeling patients with somatoform disorder or as "somatizers" because of current limitations of diagnostic testing and disease criteria.[21]

Pilowsky[24] suggests that a hallmark of abnormal illness behavior is extreme difficulty accepting advice from a physician if it doesn't fit the patient's appraisal of his or her health status. Avoidance of dualism in pain (i.e., the pain is either in the body or the mind) is key in assessing and treating individuals with pain conditions and is especially pertinent when treating individuals with psychiatric illnesses.

Table 4.
Summary: General Clinical Questions to Ask to Assess Psychosocial Aspects of Pain

Psychosocial Aspects of Pain	Clinical Questions to Ask
Global question	How is the pain affecting your life?
Emotional reactions	What's your mood generally like?
Suicidal thoughts	Do you ever feel like giving up? Do you have suicidal thoughts?
Cognitions, coping, beliefs about pain	How do you cope with the pain?
Behavioral reactions	What do you do when you have a flare up of pain?
Family functioning	How do your family members/supportive others respond when you have pain?
Social and occupational functioning	How are work and social activities going?

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V.

Types of Pain

ACUTE PAIN

Postoperative Pain

Postoperative pain is arguably the most commonly occurring model of an acute pain condition. Despite its high prevalence, postoperative pain continues to be a challenging condition to treat, even in the face of continuing advances in pain management. The Joint Commission on Accreditation of Healthcare Organizations has developed guidelines for pain management specifically to try to improve consistency and effectiveness of pain care. These guidelines make clear recommendations on not only the importance of treatment of pain in hospitalized patients, but also continued assessment and reassessment of patients to uphold quality of pain management. Yet, a 2003 national survey revealed that 80% of adults surveyed who had undergone major surgery reported pain that was moderate to severe despite treatment with analgesics.[1]

Acute postoperative pain is likely managed by the pain service, anesthesiologist, or surgeon. Specific types of postoperative pain and their individual treatments fall beyond the scope of this manual.

In the event that the responsibility of postoperative pain management falls on the shoulders of the primary care practitioner, some basic steps and considerations should be kept in mind that can improve the likelihood of effective treatment:

- Preoperative discussion should take place with the patient (if possible) to increase awareness of expectations of pain and its management and minimize stress.
- Detailed knowledge of use of analgesics before surgery if applicable is important to estimate analgesic needs.

- Preemptive therapy may actually decrease postprocedure requirements for analgesics:
  - Nonsteroidal antiinflammatory drugs
  - Cyclooxygenase-2 (COX-2) inhibitors (highly used for preemptive therapy in the past are now only valuable in selected patients where the benefit is clear and the patients are appropriate candidates)
  - Local anesthetics by direct injection
  - Opioids
- Multimodal analgesic techniques listed above using more than one method of pain management at the same time can reduce the amount of medications necessary to relieve pain and can minimize uncomfortable side effects of any given medication.

Adequate postoperative pain management is an integral part of medical care in the postoperative period. Benefits of good postoperative pain management include the following:

- Improved patient comfort
- Improved patient satisfaction
- Decreased time to ambulation
- Decreased rates of surgical complications
  - Bowel motility
  - Thrombophlebitic episodes
  - Improved blood flow and wound healing
  - Improved lung mechanics and severity of atelectasis
- Decreased length of hospital stay (nonambulatory patients)
- Decreased return to hospital rates (ambulatory patients)
- Decreased cost of care

CHRONIC PAIN

Back and Neck Pain

The structural framework of the neck and back consist of the vertebrae, musculature, and ligaments. As already stated, the likelihood is

that four out of five people will experience some type of back pain in their lives.[2] The epidemiology of neck and back pain is vast. Back pain is also one of the most common forms of chronic pain in patients at all age ranges.[3] Low back pain (LBP) is well-distributed across sex, race, and marital status,[4] and it is among the top 10 complaints of patients older than 16 years of age who present to the primary care practitioner,[5] with a prevalence of up to 20%.[6] Although neck pain often receives less publicity than LBP, millions of people still experience neck pain and/or related arm pain at some point in their lives.

The economic and social magnitude of the impact of neck and back pain—most frequently chronic LBP—is enormous. Although it is difficult to calculate exactly how much back pain costs in the United States, the statistics show that backaches result in the loss of approximately 175 million work days and in a $20 billion loss in productivity. Two percent of the U.S. work force suffers from chronic back pain, costing the U.S. economy a total of $50 billion annually. Backaches are the second most common reason Americans go to the doctor (headaches are the first) and among the most common reasons for surgery (National Institutes of Health data on file).[7]

Temporal Classification of Back and Neck Pain

Acute back or neck pain generally arises spontaneously and usually lasts from a few days to a few months. Such pain may or may not have radicular symptoms associated with it. Treatment for acute back and neck pain is usually symptomatic and typically includes activity as tolerated and some form of analgesia. Bed rest for more than 2 days has now been shown conclusively to worsen prognosis. In fact, the debunking of the myth that rest is helpful, with the consequent reduction of iatrogenic disability, is probably the major advance in the treatment of back pain in the modern era.[8] The reader is referred to Chapter IV for detailed discussion of treatment options for back and neck pain.

Persistent, or *chronic*, back or neck pain may be defined as pain that lasts 3–6 months or longer and does not improve over time. In

cases of chronic back pain, there is a high correlation with spondylotic disease. Patients with persistent pain often undergo surgical intervention,[9] although results are inconsistent. It has been recently appreciated that many patients have neither acute back pain nor chronic persistent back pain, but instead have recurrent back pain, or constant back trouble that occasionally becomes severe and disabling. These patients may experience long-term difficulties, including psychological and medical comorbidities. Some common psychological problems include depression, anxiety, and sleep disturbance. Multidisciplinary interventions, emphasizing rehabilitation, are commonly required.

Common pathologic causes of back and neck pain include the following:

- Disc herniation
- Sciatica
- Torticollis
- Spinal stenosis
- Spondylosis
- Spondylolisthesis
- Cauda equina syndrome
- Cancer
  - Primary tumor
  - Metastatic lesion
- Osteomyelitis of the spine
- Injury (e.g., fracture, compression)
  - As a direct result of trauma
  - As a result of osteoporotic disease

Making the diagnosis in cases of chronic back and neck pain can be challenging for primary caregivers and experts alike. Although diagnostic procedures have continued to improve in their accuracy and reliability, up to 85% of chronic cases may end up with no definitive diagnosis.[10] Sometimes the identifiable causes are muscular, but in the face of accompanying neurologic deficit, there may indeed be some degree of neurologic etiology. Although sometimes

episodes of back and neck pain have no identifiable anatomic cause, there are many cases where this pain can be linked to a known cause, such as the following:

- Overuse, strenuous activity, or improper use such as repetitive or heavy lifting
- Muscle injury
  - Strain
  - Torticollis
- Whiplash (sudden force injury)
- Concurrent diagnosis of cancer
- Trauma
  - Injury/contusion
  - Fracture
- Degeneration of vertebrae, often caused by stresses on the muscles and ligaments that support the spine or the effects of aging
- Infection
- Abnormal growth, such as a tumor or bone spur
- Obesity with the result of increased weight on the spine and pressure on the disks
- Poor muscle tone
- Muscle tension or spasm
- Ligament or muscle tears
- Joint problems such as arthritis
- Protruding or herniated disk and/or nerve impingement
- Osteoporosis and compression fractures
- Congenital/developmental abnormalities of the vertebrae and bones (i.e., scoliosis)

Evaluation of Low Back Pain

Assessment of LBP should begin with a detailed history of the pain, including the patient's perception of its cause and the location and duration of the pain. A careful history is necessary to formulate diagnostic impressions and determine what the cause of the pain is. The most important goal in assessing the patient with LBP is to rule

out "diagnostic imperatives,"—that is, serious illnesses that can present with LBP. These include dissecting aortic aneurysm, cancer or infections involving the spine, inflammatory spondylitis, and referred pain from the abdominal or pelvic viscera. Factors that suggest the need to rule out such disorders include new-onset back pain in an older patient, systemic symptoms (e.g., fever, sweats, and weight loss), history of cancer, and abdominal or pelvic pain.

During the physical examination, observe the patient's gait and overall posture. Scoliosis may point to underlying muscle spasm or neurogenic involvement. The examiner should also test the patient's spinal range of motion. Although the reliability of provocative maneuvers is not high, reproduction of pain on lumbar flexion tends to indicate disk pathology; pain on extension suggests facet joint pathology. The examiner should also palpate the spine for point tenderness, which could help determine the site of pathology. Palpation of the abdomen and pelvis and examination for signs of systemic illness are imperative in the evaluation of all patients with acute or subacute LBP, especially with the risk factors noted above.

Suspicion of lumbosacral radiculopathy, suggested by radiating pain or by accompanying neurologic symptoms, can be confirmed with provocative maneuvers. In the straight leg raise test, pain radiating below the knee when the leg is raised between 30 and 60 degrees suggests nerve root irritation. The straight-leg raise test is used as a test for sciatica, the lay term for *lumbosacral radiculopathy*. The crossed straight leg raise test, which tests/assesses for pain radiating down the contralateral leg when the ipsilateral leg is raised, is a less sensitive, but highly specific test for lumbosacral radiculopathy.[11] A focused neurologic examination should be performed. More details can be found in Chapter IV. Reflexes (knee and ankle) and motor and sensory testing should also be conducted to determine the presence of a neurologic deficit, which could indicate lumbosacral radiculopathy, cauda equina syndrome, or even spinal cord involvement.

Laboratory tests are not usually needed during an initial evaluation of LBP. However, if risk factors suggest tumor or infection, appropriate blood work and imaging studies must be obtained.

Table 5.
Treatment of Back and Neck Pain

Once the diagnostic imperatives have been ruled out, treatment is symptomatic and is directed toward providing pain relief and restoring function.

- Most patients benefit from **maintenance of activity as tolerated, keeping as active as they can**.
- This process is often best directed by a physical therapist.

Nonsteroidal antiinflammatory drugs are helpful for acute low back pain, given the potential risks outlined in Chapter IV.

A short course of **opioid analgesics** is often required, although it is easy to overestimate their efficacy.

- A patient who cannot stand up due to acute low back pain may not stand much better while taking opioids. However, opioids can facilitate more comfortable rest periods and can facilitate reintroduction of activity and exercise.

Muscle relaxants are frequently prescribed for acute low back pain and probably have analgesic efficacy, although they do not have any primary effect on muscles. Although physicians attempting to avoid opioid use often prescribe muscle relaxants, little is accomplished for the patient by this approach because the muscle relaxants share most of the liabilities of the opioids.

The benefits of **nonpharmacologic approaches** should not be underestimated—a well-constructed comparative trial has now shown that a heating pad provided more analgesia than a nonsteroidal antiinflammatory drug.[10]

Many practitioners perform **epidural steroid injections** on patients with acute sciatica to reduce nerve inflammation and prevent chronicity, although this approach has never been validated.

- **Oral steroids are generally *not* indicated** for the treatment of back and neck pain.

Antidepressants have been widely used for both depressed and nondepressed patients with chronic low back problems. The extent to which these medications are used in treating patients with acute low back problems is unknown. Some researchers have hypothesized that the medications may possibly have a pain-relieving effect in addition to antidepressant properties. If so, the medications could help some patients who have chronic pain whether or not the patients are also depressed. The therapeutic objective of using antidepressant medications for low back problems is to reduce pain (See more discussion of antidepressants in Chapter VI.)

(continued)

Table 5.
Treatment of Back and Neck Pain (Continued)

Because the progression of low back pain from acute to chronic is a major problem, it is worth keeping in mind strategies for prevention of this progression. The major risks for chronicity are psychosocial: comorbid psychiatric disorders, previous disabling episodes, poor job satisfaction, and so forth. It is advisable to perform a psychosocial assessment screening on patients with acute low back pain so that high risk patients can be promptly referred for multidisciplinary rehabilitative management, with vocational rehabilitation if needed.

Headache

The most common of all pain syndromes is headache. As stated previously, studies show that the large majority of adults experience headaches and that headache pain is the single largest factor in work absenteeism as well as total expenditures for health care costs.

Headaches are usually characterized by attacks that are separated by symptom-free intervals, but sometimes may become chronic. Headaches can be caused by structural abnormalities, sinus disease, increased intracranial pressure, or even referred pain from the cervical spine.

The following are three major hypotheses concerning the various origins of headache:

1. Neurogenic or vascular abnormalities in the brain
2. Myofascial or skeletal mechanisms from the cervical spine
3. A variety of diseases involving the face

The ability to make a rapid and accurate diagnosis is crucial to the successful management of any headache disorder. Because head pain can have many causes, a rational approach facilitates differential diagnosis and may increase the likelihood of a positive therapeutic outcome.

Classification of Headaches

Headaches are commonly classified as either primary or secondary. The *primary headache* disorders—those *not* associated with an underly-

ing pathology—include migraine, tension-type, and cluster headache. *Secondary headache* disorders—those attributed to an underlying pathologic condition—include any head pain of infectious, neoplastic, vascular, drug-induced, or idiopathic origin. The vast majority of patients who present with headache have one of the primary disorders, as serious secondary causes for presentation with head pain are rare.

A number of diagnostic schemata for headache have been proposed. As early as 1962, for example, the Ad Hoc Committee on Classification of Headache listed the features that are typically present during certain types of headache, but it failed to indicate which features or combinations of features were required to establish a diagnosis. By 1988, recognizing the need for improvement in headache classification, the *International Headache Society (IHS)* published a new system, the second edition of the International Headache Classification (ICHD-2).

The following information is based on and adapted from the updated IHS criteria, ICHD-2, which outline the classification, incidence, and prevalence, and specific characteristics necessary to confirm a broad range of headache disorders.[12]

Primary Headache

Migraine Headache. Migraine is a chronic neurologic disorder characterized by episodic attacks of head pain and associated symptoms. Similar epidemiologic studies conducted 10 years apart show that the prevalence and distribution of migraine have remained stable over the last decade in the United States, with approximately 18% of women and 6% of men satisfying diagnostic criteria for the condition. Studies conducted outside the United States are in agreement with these migraine prevalence rates. Even though it is widespread, migraine remains underdiagnosed; only 48% of Americans who satisfy criteria for migraine reported receiving a physician diagnosis of migraine. Many patients never even seek medical advice and treat themselves with over-the-counter medications for this condition. The IHS recognizes six variants of migraine, but the most common types seen in primary care practice are migraine with aura (formerly "classic" migraine), migraine without aura (formerly "common" migraine), and probable migraine (formerly "migrainous headache").

Table 6.
Adapted International Headache Society Criteria for Migraine

Migraine with Aura	Migraine without Aura* (At Least Any Two Descriptions)	Migraine without Aura* (At Least Any One Symptom)
Visual symptoms Blind spots Flashes of light "Zigzag" light Other visual distortions Motor weakness Sensory symptoms Paresthesia Aphasia Signs of brain stem dysfunction Diplopia Ataxia Vertigo	Unilateral nature Pulsatile quality of pain Moderate to severe intensity Aggravation by, or causing avoidance of routine physical activity	Nausea and/or vomiting Photophobia Phonophobia

*Patients without aura must have five attacks fulfilling the above criteria, with headaches lasting 4–72 hrs and no signs of a secondary headache disorder, to meet criteria.

Migraine with Aura. Providers should suspect migraine with aura whenever a headache is preceded by one of the neurologic symptoms listed in Table 6.

The symptoms of migraine with aura should be reported as fully reversible, developing over 5–20 minutes and lasting less than 60 minutes. It is commonly observed in clinical practice that not all auras are followed by a headache or a headache that is associated with characteristics of migraine. If aura occurs without subsequent headache, then the condition is a typical aura without headache; if a

nonmigraine headache follows aura, then it is classified as a typical aura with a nonmigraine headache.

Migraine without Aura. Migraine without aura is the commonest subtype of migraine. It has a higher average attack frequency and is usually more disabling than migraine with aura. Migraine without aura is characterized by headache pain that is virtually indistinguishable from the pain experienced by patients with aura, except no aura precedes the migraine attack.

Migraine without aura often has a strict menstrual relationship. In contrast to the first edition of *The International Classification of Headache Disorders*, the current edition gives criteria for *pure menstrual migraine* and *menstrually related migraine*, but in the appendix because of uncertainty over whether they should be regarded as separate entities. Because of their frequency, and menstrual relationship, they deserve mention. *(Readers are encouraged to visit http://www.PainEDU.org for more detailed information on migraine headaches and their menstrual relationship.)*

Pure Menstrual Migraine. Pure menstrual migraine has the following distinguishing characteristics:

- Attacks in a menstruating woman
- Fulfilling criteria for migraine without aura
- Attacks occur exclusively on day 1 ± 2 (i.e., days –2 to +3) of menstruation in at least two out of three menstrual cycles and at *no other times of the cycle*

Menstrually Related Migraine. Menstrually related migraine has the following distinguishing characteristics:

- Attacks in a menstruating woman
- Fulfilling criteria for migraine without aura
- Attacks occur on day 1 ± 2 (i.e., days –2 to +3) of menstruation in at least two out of three menstrual cycles and *in addition at other times of the cycle*

Because migraine without aura does not have a single distinguishing feature, the IHS criteria for migraine without aura require the presence of a constellation of symptoms (see Table 6).

Despite the existence of specific criteria of both types of migraine, clinicians frequently misdiagnose migraine. One reason for error is the criteria themselves. The IHS criteria do not include all symptoms frequently observed in episodes of migraine. Consequently, migraine associated with muscle or neck pain, a non-IHS migraine diagnostic criterion, is often diagnosed as tension-type headache (TTH), or migraine associated with nasal symptoms such as rhinorrhea and nasal congestion, also not included as IHS diagnostic criteria, is diagnosed as a "sinus" headache. In both cases, research demonstrates that these headaches are usually migraine. Additionally, clinicians often focus on the presence of a single symptom to make a migraine diagnosis. This often results in even experts having different opinions of whether or not a headache is truly a migraine.

An especially significant complicating factor in the diagnosis of migraine may be the existence of comorbid illness. Migraine has been associated with a number of psychiatric and medical-neurologic illnesses. Therefore, providers should not be surprised to find an increased incidence of affective and anxiety disorders among migraine patients. Bipolar psychiatric disturbances and phobias are also noted. The incidence of stroke, epilepsy, essential tremor, mitral valve prolapse, and Raynaud's disease also are increased in migraine patients compared with their nonmigraine counterparts. *(Readers are encouraged to visit http://www.PainEdu.org for more detailed information on migraine headaches.)*

Table 7.
Treatment of Migraine Headache Pain

1. Treatment should be adapted to the patient's individual needs, in view of his or her medical history and mental health.
2. Migraine treatment strategies are often considered to be one of two approaches:
   a. **Abortive treatment** (getting rid of an acute headache)
   b. **Prophylactic treatment** (preventing them)

(continued)

Table 7.
Treatment of Migraine Headache Pain (Continued)

3. First, **precipitating factors should be identified** so that the patient can learn to **avoid them**, if possible. These factors include the following:
   a. Alcohol
   b. Abrupt changes in climate or weather
   c. Diet
   d. Missing meals
   e. Stress
   f. Hormonal changes (including menstruation, ovulation, and menopause)
   g. Lack of sleep
4. **Teaching** the patient coping skills is also helpful.
5. **With regard to acute measures, all of the treatment strategies are more effective when combined with treating coexisting insomnia.**
6. **Nonsteroidal antiinflammatory drugs** or **high doses of aspirin** are effective in treating migraine.[13] However, the gastrointestinal side effects of such medications may require that they be administered through the rectal or parenteral route. Moreover, an antiemetic may be needed to counteract the effects of treatment.
7. **Serotonin (5-HT) agonists** (e.g., triptans such as sumatriptan, rizatriptan, and zolmitriptan) are the most effective drugs for aborting a migraine episode. **Sumatriptan** is the most commonly prescribed triptan; however, it also has many side effects. Triptans are contraindicated for patients with cardiovascular or cerebrovascular disorders because of their vasoconstrictive action.
8. Other options for acute treatment of migraine include **antiemetics** and **intranasal dihydroergotamine**.
9. Although **ergotamine** treatments were commonly used to treat migraines in the past, they are generally used only for headaches that have been resistant to other treatments.[14]

(continued)

Table 7.
Treatment of Migraine Headache Pain (Continued)

10. Prophylactic treatments of migraine are usually considered in cases where the patient's migraines are frequent and disabling, a common rule being more than three severe headaches per month. Research indicates that the long-term efficacy of prophylactic measures is only about 55%.
    a. Prophylactic treatment may also be beneficial in cases of menstrually related migraines, with drugs such as **frovatriptan**.
    b. Other drugs found effective for preventing migraine that may be considered despite the occurrence of side effects that may make them more or less reasonable for a given patient include the following:
        i. **Beta blockers**
        ii. **Sodium valproate**
        iii. **Gabapentin**
        iv. **Serotonin antagonists**
        v. **Calcium channel blockers**
    c. Nonpharmacologic treatments, including **biofeedback**, **behavioral therapy**, and **acupuncture**, are also effective in preventing migraine headaches.[13,14]

Tension-Type Headache. TTH is the *most common* type of primary headache. In the general population, estimates by the IHS of the prevalence of episodic TTH vary widely, from 30 to 80%. The IHS criteria for TTH, listed in Table 8, outline a range of specific characteristics that distinguish TTH from migraine and show that the symptoms tend to be less severe, bilateral, nonpulsating, and not aggravated by routine physical activity. Symptoms associated with migraine attacks, such as nausea, phonophobia, or photophobia, are rarely present, but there can be symptomatic overlap. Studies have shown that 25% of TTH patients also have migraine, and 62% of migraineurs have TTH. Moreover, epidemiologic research suggests that TTH, when it coexists with migraine, might represent a segment on the continuum of the same disorder.

In the 2004 IHS diagnostic criteria, episodic TTH, as opposed to chronic daily TTH, is a condition without associated symptoms other than photophobia or phonophobia. Although this further sep-

Table 8.
Adapted International Headache Society Criteria for Tension-Type Headache*

Description (At Least Any Two Descriptions)	Associated Symptoms (At Least One)
Pressing or tightening	Absence of nausea or vomiting
Mild to moderate intensity	Photophobia *or* phonophobia (not both)
Bilateral location	
No worsening with exertion	

*Must have had more than 10 previous headache episodes and no evidence of a secondary headache disorder.

arates migraine and tension headache, it leaves more headache presentations of a mixed type. Much of the void is filled by a diagnosis of "probable migraine," which represents a headache that lacks one diagnostic criterion for migraine headache.

Table 9.
Treatment of Tension-Type Headache Pain

1. Research shows that **nonsteroidal antiinflammatory drugs** are the primary treatment of choice for acute tension-type headaches.[14]
2. **Combining analgesics with caffeine or sedatives** may be more effective than analgesics alone.
3. **There is no scientific evidence that muscle relaxants are an effective treatment.**
4. Tricyclic antidepressants are often prescribed as prophylactic treatment for chronic tension-type headaches. **Amitriptyline** is the most frequently prescribed antidepressant, but it has many side effects. When the patient experiences these side effects, some other antidepressants, such as **nortriptyline or desipramine**, can be used.
5. **Cognitive-behavioral strategies** are also effective for reducing stress, and research shows that these strategies are most effective when combined with **biofeedback or relaxation techniques**.
6. Some other nonpharmacologic treatments include **massage, positioning, and heat or cold applications**.

Cluster Headache. Cluster headaches are the third major type of primary headache and are defined as a strictly unilateral headache, usually occurring once or a few times a day at a characteristic time (e.g., 1 a.m.), lasting for 15–180 minutes, occurring in a series which lasts from several weeks to several months, separated by remissions lasting from months to years.

Findings from prevalence studies of cluster headache are controversial. Patients with cluster headaches generally rate the intensity of their pain as among the worst imaginable, and cluster headache may be the *most severe* of the primary headache disorders. Most often, cluster headache occurs once every 24 hours for 6–12 weeks at a time, with remission periods typically lasting 12 months. Typical age of onset for both men and women is 27–31 years. However, *cluster headaches are one of the few headache syndromes that are more frequent in men than in women*. Population studies of cluster headaches find the occurrence is five times more likely in males. Cluster headaches may be related to cigarette smoking, head trauma, and positive family history for cluster headaches.

Cluster attacks have several differentiating features. Most important of these is the presence of transient autonomic symptoms. These features are listed in Table 10.

Table 10.
Adapted International Headache Society Criteria for Cluster Headache*

Description (All Four Descriptions)	Autonomic Symptoms (Any Two Symptoms)
Severe headache	Rhinorrhea
Unilateral and ipsilateral quality	Lacrimation
Duration of 15–180 mins	Facial sweating
Orbital, periorbital, or temporal location	Miosis
	Eyelid edema
	Conjunctival injection
	Ptosis

*No evidence of a secondary headache disorder.

Table 11.
Treatment of Cluster Headache Pain

1. **In most cases, patients with cluster headaches should be referred to a specialist.**
2. Acute treatment of cluster headaches includes the following:
   a. Inhalation of **100% oxygen**
   b. Intranasal application of **dihydroergotamine**
   c. Subcutaneous injection of **sumatriptan**
3. There is *no consensus as to prophylactic treatment* of cluster headaches. Some methods include prescribing the following:
   a. **Verapamil**
   b. **Lithium carbonate**
   c. **Methysergide**
   d. **Ergotamine**
   e. **Corticosteroids**

Systemic symptoms, such as bradycardia, hypertension, and increased gastric acid production, may also accompany an attack. Another unique feature is that cluster episodes are *always* on the same side, even when long intervals separate headache episodes.

Diagnosis of Primary Headache in Clinical Practice

Because most office-based evaluations of headache occur when patients are asymptomatic, the primary health care provider relies on *impact-based recognition of headache*. On those occasions when a person is being evaluated during a headache, it is best to rely on IHS criteria, summarized in Table 12.[12]

Given the constraints of clinical practice, however, primary headache disorders can be quickly and reliably recognized by inquiring about the following:

- Interference with daily living
- Recurrent disabling headaches should be considered migraine until proved otherwise

Table 12.
Characteristics of Primary Headache Disorders

	Migraine	Tension-Type	Cluster
Location	Unilateral	Bilateral	Strictly unilateral
Intensity	Moderate/severe	Mild/moderate	Severe
Duration	4–72 hrs	30 mins to 7 days	15–90 mins
Quality	Throbbing	Pressing/tightening	Severe
Associated symptoms	Yes	No	Yes, autonomic
Gender	Female > male	Female > male	Male > female

- Frequency
  - The frequency of headaches alerts the clinician to chronic headache disorders and migraine transformation
  - Daily or near-daily headache patterns should alert the provider to the possibility of medication overuse
- Change in headache pattern over prior 6-month period
  - A negative response reassures the caregiver and the patient that serious underlying disease is unlikely
  - An affirmative answer indicates the need for a more in depth evaluation of possible warning signs that a secondary headache disorder may be present
- Change in existing headaches
  - "Worst headache ever"
- Focal neurologic signs or symptoms such as the following:
  - Papilledema
  - Motor weakness
  - Memory loss
  - Papillary abnormalities
  - Sensory loss
- Association with systemic symptoms

- New-onset headache after age 50
- Medication use
  - More than 2 days a week
    - Overuse of any acute headache remedy, prescription or nonprescription, *may promote more frequent headaches*
      - "Medication-induced migraine"

Secondary Headache

As mentioned in "Classification of Headaches," secondary headache disorders are those attributed to an underlying pathologic condition. Obviously, the focus centers around the headache-causing condition when dealing with diagnosis.

The breakdown of conditions that cause secondary headache identified by the IHS are the following:

- Head and/or neck trauma
- Cranial or cervical vascular disorder
- Cranial nonvascular disorder
- A substance or its withdrawal
- Infection
- Homeostasis
- Disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structure
- Psychiatric disorder

The following criteria should be used for assistance in diagnosis and distinguishing secondary from primary headache:

- Another disorder known to be able to cause headache has been demonstrated.
- Headache occurs in close temporal relation to the other disorder, and/or there is other evidence of a causal relationship.
- Headache is greatly reduced or resolves within 3 months (possibly shorter for some disorders) after successful treatment or spontaneous remission of the causative disorder.

Arthritis Pain

In 2002, 43 million American adults reported doctor-diagnosed arthritis, making arthritis one of the nation's most common health problems. As a result of this, arthritis is very commonly seen in primary care practices. Obviously, as the U.S. population ages, these numbers are likely to increase dramatically. The number of people who have doctor-diagnosed arthritis is projected to increase to 67 million in 2030.[15]

Arthritis is actually not a single disease, but a constellation consisting of more than 100 different conditions. Among the most common are osteoarthritis (OA) and rheumatoid arthritis (RA). Considering the costs associated with diagnosis, treatment, and lost productivity due to disability, arthritis is one of the most expensive diseases in the United States today.[16,17] Arthritis is actually the nation's leading cause of disability, limiting everyday activities for 16 million Americans in 2002. Work limitations attributable to arthritis affect more than 5% of the general population and nearly 30% of people with arthritis. Each year, arthritis results in 750,000 hospitalizations and 36 million outpatient visits. Direct medical costs for arthritis were more than $51 billion in 1997. Arthritis is not just an old person's disease. Nearly two-thirds of people with arthritis are younger than age 65.[17]

Osteoarthritis

OA is the most common arthritic condition, affecting from 16 million to 23 million Americans usually 60 years of age or older.[17,18] OA is primarily a disease of the cartilage that produces local tissue response, mechanical change, and ultimately, failure of function.

The joints most commonly involved in presentation of OA typically include the following:

- Cervical spine
- Distal interphalangeal joints
- Feet and ankles
- First carpometacarpal joints
- Hips
- Knees

- Lower spine
- Proximal interphalangeal joints

Patients usually present with symptoms of *morning stiffness lasting no longer than 20–30 minutes*. Presence of stiffness that persists longer should generate inquiry about other possible diagnoses. In the absence of injury, involvement of the shoulders, wrists, and elbows is uncommon.

Diagnosis of OA is assisted by attention to the following:

- Clinical presentation
  - History and physical findings
- Radiographic evaluation
  - Joint-space narrowing of large, weight-bearing joints
  - Increased subchondral bony sclerosis
  - Osteophytes
  - Small synovial effusions with noninflammatory pathology findings
  - Laboratory tests are usually *not* useful and often normal

Rheumatoid Arthritis

RA is the second most common form of arthritis. It is a debilitating and destructive disease and, unlike OA, a systemic inflammatory condition. Women are affected more than men (5:1). Incidence is highest between ages 20 and 50, with a prevalence of 1–2% of adults, ranging from 0.3% in patients younger than 35 to approximately 10% of those older than 65 years old.[18]

RA is a chronic autoimmune disease; patients present with findings including the following:

- Symmetric involvement of small and large joints with the following:
  - Pain
  - Swelling
  - Warmth
  - Tenderness
  - Synovitis

Table 13.
Quick Comparison of Osteoarthritis vs. Rheumatoid Arthritis

Osteoarthritis	Rheumatoid Arthritis
Usually occurs in patients 60 years or older	Highest incidence between ages 20 and 50
Asymmetric joint involvement	Symmetric joint involvement
Distal and proximal interphalangeal joints	Small and large joints
Lumbar and cervical spine	Large joint effusion
Weight-bearing joints	Inflammatory
Small joint effusion	Stiffness lasts hours to full day
Not inflammatory	Laboratory tests useful
Morning stiffness lasts 20–30 mins	Elevated erythrocyte sedimentation rate
Laboratory tests not useful	Elevated C-reactive protein
Radiographic evidence	Anemia of chronic disease
Joint space narrowing of large, weight-bearing joints	Rheumatoid factor present in 90% of patients
Increased subchondral bony sclerosis	Radiographic evidence
	Variable

- Occurs in patients typically younger than OA patients
- Morning stiffness lasts several hours to entire day
- Fever
- Weight loss

Diagnosis of RA is assisted by attention to the following clinical presentation:

- History and physical findings
  - Chronic progressive system inflammation
    - Joint swelling
    - Synovitis
- Large joint effusions

- Pathology positive for the following:
  - Elevated white blood cell count (20,000–50,000) with 50–70% polymorphonuclear leukocyte cells
- Laboratory tests
  - Elevated erythrocyte sedimentation rate
  - Elevated C-reactive protein
  - Anemia of chronic disease
  - Rheumatoid factor present in 90% of patients
- Radiographic studies
  - Juxtaarticular osteoporosis may be present
  - Symmetric affectation

In addition to arthritis' structural and mechanical consequences, pain is a significant stress for people with arthritis. People with OA and RA experience both acute and chronic pain, depending on the progression of their condition. A major consideration in dealing with arthritis patients is the patient's level of function, as it is often the criterion by which treatment successes are measured. This functionality is influenced by physical as well as psychosocial factors.

Because patients with arthritis will live the remainder of their lives with some degree of their condition, this, indeed, could be one of the most common chronic painful conditions faced in primary care practices today and in the future. Although they are quite different conditions, treatment strategies of OA and RA are similar. These strategies include those listed in Tables 14 and 15.

Table 14.
Treatment of Arthritis Pain

1. Patient education
   a. Weight reduction
   b. Physical exercise
   c. Cognitive-behavioral therapy
      Self-help techniques
   d. Good nutritional habits

(continued)

Table 14.
Treatment of Arthritis Pain (Continued)

2. Assistive devices
3. It is clear that altering the progression of disease in rheumatoid arthritis (RA) has importance in controlling pain. In RA, these drugs are often the first line of therapy. Disease-modifying medications commonly used to achieve this goal include the following:
   a. Methotrexate
   b. Leflunomide
   c. Tumor necrosis factor (TNF-α inhibitors)
   d. Sulfasalazine
4. Topical agents may be beneficial in helping to abate arthritis-related pain.
   a. Capsaicin
   b. Lidocaine 5% patch
5. Hyaluronic acid viscosupplementation may be useful in treating osteoarthritis (OA) and is Food and Drug Administration–approved for OA of the knee.
6. Analgesics
   a. Acetaminophen (in the absence of signs of inflammation)
   b. Nonsteroidal antiinflammatory drugs
      i. Nonspecific nonsteroidal antiinflammatory drugs (Consider coadministration of proton pump inhibitor for gastric protection.)
      ii. Cyclooxygenase-2–selective nonsteroidal antiinflammatory drugs (only in appropriate patients)
   c. Intraarticular injection of glucocorticoids in patients with OA with significant inflammation
   d. Systemic glucocorticoids should be avoided in treatment of OA but may be useful in low doses and short-term use in treatment of RA.
      i. Should be combined with osteoporosis prophylaxis:
         - Bisphosphonates
         - Calcium supplementation
         - Vitamin D supplementation

(continued)

Table 14.
Treatment of Arthritis Pain (Continued)

7. Opioids should be used in patients with OA or RA when other medications or nonpharmacologic approaches provide inadequate pain relief and affect the patient's quality of life. These include but are not limited to the following:
   a. Morphine
   b. Oxycodone
   c. Oxymorphone
   d. Hydrocodone
8. Tramadol, like opioids, may be effective in treating pain in OA and RA that has been refractory to other treatments.

   Opioids and tramadol may be used in combination with other medications and approaches to minimize the dosage of opioid required and therefore minimize adverse effects of these drugs.

Table 15.
Surgical Intervention

Procedures	Reasons for Surgery
Procedures such as synovectomy, arthroscopic débridement, and joint replacement surgery often have improved success rates before the development of tendon rupture, contracture, or advanced joint disease. Commonly, the decision to treat with surgical intervention is made on an individual basis with consideration of the following factors.	Pain Function Deformity Stiffness Medical risk factors Patient goals and preferences Prior treatments and successes Radiographic evidence Age Patient quality of life

Gout

Gout is one of the most painful forms of arthritis. Gout typically is an example of an acutely painful arthritic condition, as compared to OA and RA. Gout accounts for approximately 5% of all cases of arthritis. In the United States, it occurs in approximately 840 out of every 100,000 people. Gout is nine times more common in men than women. Gout often affects men in their 40s and 50s, although gout attacks can occur after puberty, which sees an increase in uric acid levels. Gout attacks are more common in women after the menopause.

Gout is thought to occur from buildup of uric acid in the body, resulting in the following:

- Sharp uric acid crystal deposits in the joints, typically the big toe
- Tophi, deposits of uric acid under the skin, appearing as hard lumps
- Uric acid renal calculi

Although the first attack of gout often occurs in the big toe, it can also occur in other locations, such as in the following:

- Ankles
- Elbows
- Fingers
- Heels
- Instep
- Knees
- Wrist

Commonly, gouty "attacks" can be brought on by stress, alcohol consumption, an acute illness, or even medications. The attacks can last from 3 to 10 days and may be separated from each other by months or even years. Presentation of a gouty attack is usually characteristic, with patients presenting with the following symptoms:

- Exquisite tenderness and pain in the big toe
  - Often awaking the patient from sleep at the time of the attack
- Redness
- Swelling

Table 16.
Treatment of Gout Pain

1. Traditionally, treatment for acute gout has consisted of **colchicine,** which can be effective if given early in the attack (best if used in the first 12 hours of acute attack).
2. **Nonsteroidal antiinflammatory drugs** can decrease inflammation as well as pain in joints and other tissues. Nonsteroidal antiinflammatory drugs have become the treatment choice for most acute attacks of gout.
3. **Corticosteroids** are important options in patients who cannot take nonsteroidal antiinflammatory drugs or colchicine. Given orally or by injection directly into the joint or intramuscularly, they can be very effective in treating gout attacks.
4. **Resting the affected joint** and applying cold compresses to the area also may help alleviate pain.

- Warmth of the affected area
- Stiffness

In addition to signs and symptoms, the clinician can test to confirm or exclude the diagnosis of gout:

- History of present illness
  - Sudden onset of 1 day of arthritic-like symptoms with redness and swelling
  - Presence in one single joint
- Determination of serum uric acid level
- Examination of joint aspirate for presence of uric acid crystals

Neuropathic Pain

Until recently, the mechanisms of neuropathic pain have been unknown. It is currently thought to be due to injury to or dysfunction of the nervous system. There are likely multiple mechanisms of neuropathic pain.[19] Possibilities include the following:

- Genetic predisposition to develop pain after nerve injury

- Alteration of the input from peripheral nerves to the dorsal horn of the spinal cord
- Aberrant growth of sympathetic fibers
- Peripheral or central sensitization
- An abnormal inflammatory response. Peripheral nerves, the spinal cord, and the brain react to the environment and change structure and function, emphasizing the plasticity of the nervous system.

Some common causes of neuropathic pain include the following:

- Alcoholism
- Amputation
- Back, leg, and hip problems
- Cancer chemotherapy
- Diabetes
- Facial nerve problems
- Human immunodeficiency virus infection or acquired immunodeficiency syndrome
- Multiple sclerosis
- Shingles [postherpetic neuralgia (PHN)]
- Spine surgery

Assessment of the patient with neuropathic pain involves the standard assessment for pain discussed in Chapter IV. The sensory qualities of neuropathic pain can also be assessed by specific self-report paper and pencil measures. Two instruments that are commonly used are the McGill Pain Questionnaire,[20] an instrument with a long history of research, and the newer, Neuropathic Pain Scale.[21] The *Neuropathic Pain Scale* is a reliable and valid measure of self-reported pain intensity, especially designed with attention to common aspects of neuropathic pain. A difference between the McGill Pain Questionnaire and the Neuropathic Pain Scale is the manner in which they are scored; the McGill Pain Questionnaire results in a composite score of sensory items and the Neuropathic Pain Scale results in 10 separate scores.

A focused neurologic examination should determine the presence of the following[19]:

- Allodynia (the sensation of pain after a stimulus that does not normally evoke pain; allodynia may be experienced by air blowing over the affected area, or light touch, such as the sensation of sheets or clothing)
  - Testing for the presence of dynamic allodynia is accomplished by lightly rubbing the area (e.g., with fingertip or a cotton swab)
  - Static allodynia is found by applying perpendicular pressure (e.g., with a pencil eraser or a cotton swab)
  - Thermal allodynia by applying warm or cold stimuli (e.g., with a test tube or tuning fork)
- Hyperalgesia (abnormally increased pain reactions elicited by stimuli that would normally *not* be painful)
  - Single and multiple pinpricks can be used to test for hyperalgesia
- Myofascial pain
  - Tightening muscles, ligaments, and tendons
- Motor deficiencies
  - Weakness
  - Ataxia
  - Decreased endurance

Laboratory tests in neuropathic pain, such as neuroradiologic tests and electrophysiologic studies, can sometimes be helpful in establishing the diagnosis but are not helpful in determining the presence or severity of pain.

Neuropathic pain can occur in many syndromes, including diabetic peripheral neuropathy (DPN), PHN, polyneuropathy, central pain syndromes (e.g., poststroke pain, phantom pain), and complex regional pain syndrome (CRPS) (types I and II). Some neuropathic pain states are associated with cancer and include those induced by chemotherapy, impingement of tumor on nerves, radiation, and postsurgical neuropathic pain syndromes (e.g., postmastectomy pain).[18] Painful polyneuropathies are often described as "burning and shooting" with "tingling and pins and needles." They generally occur in a stocking-and-glove distribution.

Treatment algorithms for neuropathic pain based on efficacy, tolerability, safety, and the results of published controlled clinical trials have been suggested by Galer and Dworkin[19] and generally include the following:

- Topical analgesics
- Tricyclic antidepressants
- Anticonvulsants
- Opioids
- Other medications (e.g., tizanidine, tramadol) and selected invasive interventions

Diabetic Peripheral Neuropathy

DPN is an often undiagnosed and tragic complication of diabetes. DPN is thought to occur as a result of microvascular insufficiency, a common complication of diabetes. Twenty-five to fifty percent of diabetic patients develop DPN in their lifetime.[22] Although it occurs so commonly, a recent survey by the American Diabetes Association indicated that for most of the respondents who experienced pain, 75% had not been diagnosed. Additionally, in 2005, 56% of symptomatic respondents were not even familiar with the term "diabetic neuropathy."[23]

DPN can have several deleterious effects on patients, not unlike other chronic painful conditions, including the following:

- Depression
- Anxiety
- Insomnia
- Decreased quality of life
  - Inability to perform activities of daily living
  - Increased disability
  - Inability to perceive dangerous conditions
    - Heat
    - Cold
    - Tissue damage

The most common form of DPN is distal symmetrical polyneuropathy of the lower extremities, manifesting itself with pain having the following qualities:

- Shooting
- Burning
- Stabbing pain in the feet or lower legs

A position statement in 2006 by the American Diabetes Association recommends screening of patients for DPN at the time of diagnosis of type 2 diabetes and 5 years after diagnosis of type 1 diabetes.[24] Screening for DPN includes examination of ankle reflexes and sensory function in the feet. Investigation should be performed to inquire about neuropathic symptoms in the feet and lower extremities, as well as physical examination for ulcers, sores, or other forms of tissue damage.

The early recognition and appropriate management of neuropathy in the patient with diabetes are important for a number of reasons:

- Nondiabetic neuropathies may be present in patients with diabetes and may be treatable.
- A number of treatment options exist for symptomatic diabetic neuropathy.
- Up to 50% of DPN may be asymptomatic, and patients are at risk of insensate injury to their feet.
- Autonomic neuropathy may involve every system in the body.
  - Cardiovascular autonomic neuropathy causes substantial morbidity and mortality.

Specific treatment for the underlying nerve damage is currently not available, other than improved glycemic control, which may slow progression but rarely reverses neuronal loss. Effective symptomatic treatments are available for the manifestations of DPN and autonomic neuropathy. Once the diagnosis of DPN is established, special foot care is appropriate for insensate feet to decrease the risk of amputation.[24]

Table 17.
Treatment of Diabetic Peripheral Neuropathy

Treatment of diabetic peripheral neuropathy (DPN) pain is similar to that of other types of neuropathic pain with some special treatments as well, including the following:

1. **Glycemic control** (paramount importance in DPN)
2. **Antidepressants**
   a. **Tricyclics**, such as amitriptyline, nortriptyline, desipramine, doxepin, imipramine, maprotine, and clomipramine
   b. **Selective serotonin reuptake inhibitors**, such as fluoxetine, paroxitene, sertraline, citalopram, and fluvoxamine
   c. **Selective norepinephrine and serotonin reuptake inhibitors**, such as venlafaxine
   d. **Others**, such as bupropion, trazodone, nefazodone, and mirtazapine
3. **Anticonvulsants**
   a. **Gabapentin** is often considered to be the first-line oral agent for the treatment of neuropathic pain
   b. **Pregabalin** (recent U.S. Food and Drug Administration approval for treatment of DPN). Its presumed pain-relieving effect at the α_2-δ subunit of the presynaptic calcium channel
   c. Others include phenytoin, carbamazepine, topiramate, and valproic acid
4. **Opioids**
5. **Topical analgesics**
   a. **Lidocaine patch 5%** (for postherpetic neuralgia)
   b. **Topical capsaicin**
6. **Duloxetine** (recent U.S. Food and Drug Administration approval for treatment of DPN). Its presumed pain-relieving effect by 5-hydroxytryptamine and norepinephrine reuptake inhibition
7. **Use of well-fitting and cushioned shoes, or athletic shoes**

Postherpetic Neuralgia

PHN is a painful condition caused by the varicella zoster virus in a dermatomal distribution (the area governed by a particular sensory nerve) after an attack of herpes zoster, usually manifesting after the vesicles have crusted over and begun to heal. Each year, approximately 1 million individuals in the United States develop shingles, or herpes zoster. Approximately 20% of these shingles patients, or 200,000 individuals, go on to suffer from PHN.

PHN is thought to result after nerve fibers are damaged during a case of herpes zoster. Damaged fibers cannot transmit electrical signals from the skin to the brain as they normally do and these signals may be erratic or even exaggerated, causing chronic, often excruciating pain that may persist or recur for months—or even years—in the area where shingles first occurred. Some research suggests that this condition is three times more frequent in the cancer patient population due to immunocompromise.[25]

Pain and temperature detection systems are hypersensitive to light mechanical stimulation, which causes severe pain even from gentle touch or pressure (allodynia). Allodynia may be related to formation of new connections involving central pain transmission neurons. Other patients with PHN may have severe, spontaneous pain without allodynia, possibly secondary to increased spontaneous activity in deafferented central neurons or reorganization of central connections. An imbalance involving loss of large inhibitory fibers and an intact or increased number of small excitatory fibers has been suggested. This input on an abnormal dorsal horn containing deafferented hypersensitive neurons supports the clinical observation that both central and peripheral areas are involved in the production of pain.

Treatments are primarily pharmacologic, as noted in "Neuropathic Pain." In addition to other modalities for treatment of neuropathic pain, the lidocaine 5% patch is a topical patch approved by the U.S. Food and Drug Administration for the treatment of PHN. It is effective and extremely well-tolerated and can be safely used in conjunction with other pharmacotherapies because there is no clinically significant absorption of lidocaine. Antiviral agents (e.g., fam-

ciclovir) may also be used, the logic being that an antiviral may shorten the clinical course, prevent complications, prevent the development of latency and/or subsequent recurrences, decrease transmission, and eliminate established latency.

Painful Polyneuropathy

Peripheral neuropathy is an umbrella term for a number of patterns of nerve involvement that include mononeuropathy, mononeuropathy multiplex, plexopathy, radiculopathy, and peripheral polyneuropathy. Polyneuropathy can be recognized by classic stocking-and-glove distribution of sensory and motor findings, which in a subgroup of patients is accompanied by pain. The most common causes of peripheral polyneuropathy are diabetes, alcohol use, vitamin deficiencies, hypothyroidism, toxins including medications, and vasculitis. Cryptogenic polyneuropathy (i.e., unknown diagnosis) is a large category; recent evidence suggests that many patients with cryptogenic polyneuropathy have impaired glucose tolerance.

Diabetes may cause a number of different types of neuropathy; peripheral polyneuropathy (discussed on pg. 72) is the most common, but other types include the following:

- Diabetic amyotrophy
- Thoracic radiculopathy
- Autonomic neuropathy
- Third cranial neuropathy

The most important goal in a patient presenting with a peripheral neuropathy is to make the diagnosis because many of the neuropathies can be resolved or stabilized with primary treatment. It is of critical importance to make a diagnosis because disorders that require prompt recognition sometimes masquerade as a "benign" peripheral polyneuropathy. Once the diagnosis is established, or concurrently with diagnostic efforts, the pain must be managed.

Management is basically pharmacologic, analogous to the approach to neuropathic pain in general. Because the area of pain is often

widespread in patients with peripheral polyneuropathy, the topical agents may be less practical than in focal neuropathies; in fact, they are increasingly used and may be helpful. The oral medication approach is analogous to other types of neuropathic pain.

Complex Regional Pain Syndrome

CRPS (*type I*), formerly referred to as *reflex sympathetic dystrophy*, is a painful condition that usually develops after minor trauma, such as a sprain, strain, or contusion. CRPS type I may also follow bony fracture, surgery, or relatively benign soft tissue injury. CRPS (*type II*), formerly referred to as *causalgia*, develops after injury to a large nerve (e.g., a gunshot wound to nerve or plexus). CRPS most commonly occurs near or at the site of injury (e.g., in one hand or foot) but can be found in other body parts and may spread from the original site. The spread of pain in CRPS can be related to myofascial dysfunction in proximal muscles or may represent a centralization of the pain process, including a somatoform process.

CRPS is usually described by patients presenting with the following complaints:

- Pain
  - Burning
  - Deep aching
  - Lancinating
- Allodynia
- Edema
- Skin color changes (e.g., mottled, red, blotchy)
- Skin temperature changes (hot or cold compared with the contralateral side of the body)
- Motor weakness
- Sweating (increased or decreased compared to the contralateral side)
- Brittle nails
- Other nonspecific skin changes (e.g., shiny or extremely dry)
- Various movement disorders affecting the involved limb

The allodynia that patients present with is a characteristic feature that often interferes with the patient's ability to tolerate clothing, air conditioning, or any type of touch in the affected area. CRPS is a clinical diagnosis, and the International Association for the Study of Pain has provided diagnostic guidelines.[26]

Treatment for CRPS involves a variety of modalities, including diagnostic and therapeutic nerve blocks, medications, and physiotherapy. Pharmacologic interventions include the following:

- Lidocaine patch (5%)
- Gabapentin or pregabalin
- Intravenous lidocaine
- Mexiletine
- Opioids
- Tricyclic antidepressants
- Tizanidine[18]

Spinal cord stimulation has been efficacious for selected individuals but is only recommended when other more conservative treatments have failed. Finally, patients with true cases of CRPS almost always require psychological treatments designed to increase their pain-coping skills, decrease negative affect (e.g., depression and anxiety), and provide support through a course of rehabilitation that is often difficult.

Pain Syndromes from Peripheral Nerve Injury

Pain syndromes as a result of direct peripheral nerve injury include the following:

- Postthoracotomy pain
  - Affects the intercostal nerves and is often described as an "aching" sensation in the distribution of the incision
- Postmastectomy pain
- Postnephrectomy pain
  - Associated with nerves in the superficial flank and is described as numbness, fullness, or heaviness in the flank

- Various pain syndromes after amputation
  - The most common types of pain after amputation are phantom pain and stump pain, which are distinguished by the location of the pain being either in the "phantom" of the amputated limb or in its stump, respectively
  - May be manifested by the following:
    - Burning dysesthesia
    - Cramping
    - Feelings of distorted posturing of the nonexistent limb

The treatment of focal neuropathic pain syndromes in general follows the World Health Organization (WHO) algorithm with a focus on neuropathic pain syndromes. Although not well-studied, interventional procedures such as scar injections with steroids or neurolytic agents (e.g., phenol or alcohol), neurolytic blocks (e.g., subarachnoid alcohol), or epidural or intrathecal analgesia, can be quite useful.

Plexopathy

Plexopathy is a major cause of pain in cancer patients. It is produced by tumor invasion or compression of the cervical, brachial, or lumbosacral plexuses or as a consequence of radiation therapy. Pain is more common in plexopathy due to tumor invasion than in radiation plexopathy, wherein general neurological deficits are more prominent. It should be noted that pain may precede overt neurologic signs in plexopathies. Distinguishing plexopathy due to tumor from plexopathy due to radiation may be difficult; in general, the distinction is based on the clinical picture, imaging studies, and electrophysiologic studies.

Pain related to the cervical plexus is usually experienced in the face or head and is described as lancinating, burning, or aching. Swallowing or head movement can intensify the pain. It is important to distinguish cervical plexopathy from epidural compression, which can be done through magnetic resonance imaging or computed tomographic imaging.

Brachial plexopathy is associated with cancers of the lung or breast, with most cases associated with upper lobe lung cancer.[27] Pain in the lower plexus usually involves pain in the shoulder that

extends to the arm and fourth and fifth digits. Pain in the upper plexus, which occurs less frequently, begins in the shoulder, lateral arm, and index finger and thumb. Brachial plexopathy is usually diagnosed by computed tomographic imaging or magnetic resonance imaging. Patients with lumbosacral plexopathy usually experience pain in the pelvis, buttock, and legs. Similar to cervical and brachial plexuses, lumbosacral plexopathy can be assessed by magnetic resonance imaging or computed tomographic imaging.

Treatment of the plexopathies, again, focuses on diagnosis, primary treatment when available, and analgesic treatment, more or less in parallel. Analgesic treatment proceeds according to the WHO ladder, described in "World Health Organization Analgesic Ladder for Cancer Pain," with a focus on neuropathic pain medications. Interventional treatments can be quite effective in plexopathy pain, which is often intractable to medical management. In particular, subarachnoid alcohol neurolysis, which is in experienced hands a relatively simple and safe outpatient procedure, relieves pain reliably for a few months in most patients. Patients may also do well with prolonged epidural or intrathecal analgesic modalities, but these procedures are in general much more difficult than the neurolytic procedures under an experienced operator.

Peripheral Polyneuropathies

Peripheral polyneuropathies can be recognized by the classic stocking-and-glove distribution of symptoms and signs, as discussed previously in the case of the noncancer patient. Peripheral polyneuropathies can be caused by chemotherapy [e.g., vinca alkaloids, paclitaxel, cisplatin (Platinol), docetaxel, and vinorelbine tartrate], nutritional deficiencies, metabolic problems, alcohol consumption, and other causes. Of course, identification and treatment, when possible, of the underlying cause of the neuropathy are the most important initial step.

Symptomatic treatment of these syndromes involves the cascade of medical treatments for neuropathic pain described on pg. 72, which may lead to implantable analgesic infusion pumps or spinal cord stimulators.

Central Pain Syndrome

Central pain syndrome is a neurologic condition caused by damage to or dysfunction of the central nervous system. This syndrome can be caused by the following:

- Cerebrovascular accident
- Brain or spinal cord trauma
- Epilepsy
- Multiple sclerosis
- Parkinson's disease
- Tumor-based causes (e.g., direct pressure, tissue infiltration)

The character of the pain associated with this syndrome varies widely and may affect a large portion of the body or may be more restricted to specific areas, such as hands or feet. The extent of pain is usually related to the cause of the central nervous system injury or damage.[28]

Patients present with the following signs and symptoms and one of the above conditions:

- Pain that is typically constant
  - Moderate to severe in intensity
  - Worsened by touch, movement, emotions, and temperature changes, usually cold temperatures
  - One or more types of pain sensations, the most prominent being burning
    - Mingled with the burning may be sensations of the following:
      - "Pins and needles"
      - Pressing
      - Lacerating or aching pain
      - Brief, intolerable bursts of sharp pain similar to dental nerve pain
- Individuals may have numbness in the areas affected by the pain

Central pain syndrome often begins shortly after the causative injury or damage, but may be delayed by months or even years, especially if it is related to post–cerebrovascular accident pain. Treatment

includes conventional agents used in managing neuropathic pain, including tricyclics, anticonvulsants, and stress reduction.

Fibromyalgia

Fibromyalgia has been recognized as a clinical condition only since 1987. It is characterized by pain, stiffness, and tenderness of the muscles, tendons, and joints. Fibromyalgia was formerly known as *fibrositis*. Considered to be one of the rheumatic diseases, its cause is currently unknown. Researchers have found elevated levels of a nerve chemical signal, called substance P, and nerve growth factor in the spinal fluid of fibromyalgia patients. Serotonin is also relatively low in patients with fibromyalgia. Studies of pain in fibromyalgia have suggested that the central nervous system may be somehow supersensitized. The painful muscle tissue involved is *not* accompanied by tissue inflammation. Therefore, despite potentially disabling body pain, patients with fibromyalgia do not develop body damage or deformity.

This very challenging condition is more common in women and tends to develop during early and middle adulthood or during a woman's childbearing years. Those who have another rheumatic disease such as lupus, RA, or ankylosing spondylitis also are at a higher risk for developing fibromyalgia.

Patients typically present with the following:

- Chronic widespread muscular pain
- Fatigue
- Widespread tenderness

Many people with fibromyalgia also experience additional symptoms such as the following:

- Morning stiffness
- Headaches
- Irritable bowel syndrome
- Irritable bladder
- Cognitive and memory problems (often called "fibro fog")
- Symptoms of temporomandibular joint disorder
- Pelvic pain

- Restless legs syndrome
- Sensitivity to noise and temperature
- Anxiety and depression
- Insomnia

Diagnosis is by process of elimination and assisted by the presence of the following:

- Widespread or total musculoskeletal pain lasting more than 3 months
- Absence of other possible conditions responsible for the complaints
- Presence of more than 11 of 18 anatomically specific tender points

A number of clinicians are concerned that patients with fibromyalgia are psychologically disturbed. This is likely due to the large number of varying complaints from these patients. The likelihood is that these patients are suffering from a high incidence of anxiety and depression as a result of their widespread chronic pain.

Treatment is with conventional therapies and usually should include an antidepressant. Investigation is taking place to see if duloxetine and pregabalin, which have both been recently approved by the Food and Drug Administration for treatment of DPN, may also be effective in treating fibromyalgia.

Myofascial Pain

Myofascial pain is defined as a syndrome consisting of pain in a muscle, which is usually in spasm, and contains taut bands and/or trigger points, palpation of which reproduces the patient's pain, often with a radiating component.[29]

Associated symptoms may include heaviness, "numbness" without neurologic signs, swelling, or decreased range of motion. Trigger points are defined as localized palpable mass within a muscle, palpation of which reproduces the patient's pain, including the radiating component.[30] Myofascial pain is a regional disorder, as opposed to fibromyalgia, which by definition is a widespread disorder. Another distinction is that fibromyalgia is characterized by tender points (which are tender, but nothing is palpable), as opposed to the trigger points of myofascial

pain. Myofascial pain is a clinical diagnosis. A variety of stress-producing stimuli have been postulated in the etiology and maintenance of myofascial pain, including physical stress (e.g., fatigue), tissue injury (major or microtrauma), physiologic state (e.g., hormonal balance, nutritional status), personality, and genetic factors.[31]

Myofascial syndromes are treated by physical interventions, such as stretching, strengthening, postural reeducation, other forms of physical therapy, and vapocoolant sprays. Cases that do not respond to conservative therapy can be successfully treated with trigger point injections of a local anesthetic, low-dose steroid, or saline. Recent reports have suggested the efficacy of botulinum toxin in the treatment of refractory cases.[32] Complaints of myofascial pain, especially in the setting of headache, LBP, and CRPS type I, are common and can result from disuse of muscles secondary to pain.

Chronic Abdominal Pain

Abdominal pain can be the result of a variety of causes that individually are beyond the scope of this manual. Some examples of causes of abdominal pain are chronic intestinal obstructive processes, which occur frequently in the setting of abdominal and pelvic cancers. Other causes include visceral tumors (primary or metastatic), venous thrombosis, omental metastases, volvulus of the small intestine, and occlusion of blood flow to visceral organs. Because the issue of decreased bowel motility is quite important in this group of patients, adjunctive treatments and medications in addition to opioids to spare the adverse effects are often used. Adjunctive treatments include subcutaneous infusion of octreotide, antispasmodic agents, and antiemetics. Interventional treatments include neurolytic procedures (e.g., celiac or hypogastric plexus block, which are contraindicated in the presence of bowel obstruction) and spinal analgesic infusions.

Cancer Pain

Although research indicates that the majority of patients with cancer experience some form of pain, pain associated with cancer is frequently left undertreated. Notably, untreated cancer pain is a major

risk factor for suicide. Even though cancer pain cannot usually be entirely relieved, several treatment strategies exist to help to alleviate much of the pain and therefore improve the patient's quality of life.

Lack of effective treatment is most often due to inadequate screening and assessment. The goals of screening are twofold:

1. To screen patients routinely to determine the presence and extent of pain
2. To make a diagnosis in patients who have pain

Various barriers in the clinician–patient interaction frequently prevent the recognition of pain when it is present, without which diagnosis and treatment can never take place. The purpose of diagnosis is, like in the case of any pain syndrome, to determine whether a primary treatment exists for the underlying cause of the pain. For example, many patients with cancer develop new sources of pain that are due to treatable infections.[33]

The patient's description of the pain leading to its categorization as *somatic*, *visceral*, or *neuropathic*, is a critical guide to treatment. In cancer pain, *somatic pain* can result from tumor invasion (by direct growth or metastasis) of the bone and muscle. *Visceral pain* commonly occurs in the setting of malignancies involving internal organ systems, such as the pancreas, uterus, or liver. *Neuropathic pain* can be caused by malignant invasion and subsequent damage or disruption of peripheral nerves, plexuses, nerve root, spinal cord, or brain. Frequently, the type of cancer pain is of mixed origin. (For further definitions of the types of pain, refer to Chapter I in the manual or the glossary.) Although opioids are helpful in many types of cancer pain, they are not necessarily the most appropriate first-line treatment for certain types of pain (e.g., mild bone pain) and in some cases are minimally effective.

A psychosocial assessment is also important. Consider the effect of the cancer diagnosis on the patient, the patient's coping responses, the patient's knowledge of pain management and concerns about using controlled substances, the economic effect of pain, and changes in mood.

The diagnostic evaluation of the cause of the pain may require blood tests, radiologic studies, or neurophysiologic testing. Finally, assessment of pain at regular intervals should be ongoing.[27]

Two common cancer pain problems include the following:

- Periprocedural pain
  - Generally as a result of biopsy or removal of the cancerous tissue or organ.
  - Treatment resembles that of any other acute source of periprocedural pain.
- Bony metastasis
  - The most common cause of pain in cancer patients and is often associated with cancers of the lung, prostate, and breast. The most common areas in which they form are in the vertebrae, pelvis, femur, and skull. In many cases, patients have multiple areas of bone metastases and therefore have multiple areas of pain. Such pain is usually described as dull and aching.
  - A diagnosis of bony metastasis is confirmed through radiographic testing.
  - Treatment consists of the following:
    - Primary treatment of the cancer
    - Radiation therapy is often widely used for metastatic bone pain and is highly effective and generally well-tolerated.
    - Pharmacologic management
      - Nonsteroidal antiinflammatory drugs may be more effective than opioids, especially for movement-associated pain.
      - Many clinicians prescribed selective COX-2 inhibitors but now recognize risks associated with these drugs. This drug class still represents a viable option in carefully selected patients.
      - Opioids and other pharmacologic treatments should be added if needed, as discussed in the "Pharmacologic Options for the Management of Pain" section in Chapter VI.
      - Patients who do not respond adequately to medical management should be referred for pain management consultation because they may respond well to intrathecal analgesia or other interventional procedures.

Treatment of Cancer Pain

The treatment of cancer pain involves both pharmacologic and nonpharmacologic interventions. In terms of pharmacologic treatment, the WHO has developed an effective guideline for titration of analgesic therapy for cancer pain, which has become known as the *analgesic ladder.*[27]

World Health Organization Analgesic Ladder for Cancer Pain. The WHO in 1990 and 1996 issued guidelines that involve the treatment of cancer pain. The guidelines are presented in a ladder formation and are referred to as the "analgesic ladder." The steps of the WHO ladder are described in Table 18 and Figure 3.

Table 18.
World Health Organization Analgesic Ladder for Cancer Pain

Step 1

The first step involves treatment of mild to moderate pain with acetaminophen, aspirin, or another nonsteroidal antiinflammatory drug. Medications should be administered as needed or round-the-clock and should be titrated upward when necessary. Adjuvant analgesics, or medications that are not generally used for pain but can have an enhancing effect on other analgesics, may also be used.

Step 2

The second step involves adding an opioid for pain that persists beyond treatment in step 1. An opioid, often codeine or oxycodone, is added to the regimen at this step (the nonsteroidal antiinflammatory drug or acetaminophen should be retained).

Step 3

The third step involves treatment with an opioid on a round-the-clock basis for persistent pain. Morphine is generally the agent of choice. Short-acting opioids are often prescribed as needed for pain as a supplement to a "background dose" of long-acting opioids. This type of dosing is called "rescue" or "breakthrough" and is given for exacerbations of pain that occur beyond the constant, background pain. Whenever possible, the same type of opioid should be given for background and breakthrough treatment.

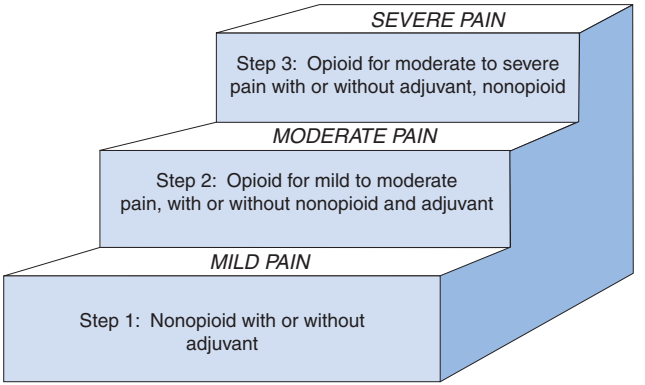

Figure 3.
World Health Organization Analgesic Ladder for Cancer Pain.

1. **The World Health Organization (WHO) approach to pharmacologic treatment contains five major concepts:**
   a. By the mouth
   b. By the clock
   c. By the ladder
   d. For the individual
   e. With careful documentation
2. In treating patients with cancer, the medication regimen should be individualized. A simple regimen should be developed, and medication should be taken orally unless the patient is unable (e.g., trouble swallowing, obtundation).
3. **Nonsteroidal antiinflammatory drugs** and/or acetaminophen should be prescribed for mild to moderate pain **(step 1 of the WHO ladder)**.
4. With persistent pain or when pain increases, **opioids** should be administered in addition to the nonsteroidal antiinflammatory drugs. The WHO guidelines initially recommended using **"weak" opioids** for initial treatment—for example, codeine, oxycodone, propoxyphene, hydrocodone, and tramadol **(step 2 of the WHO ladder)**.

5. When pain is more severe at the outset or in the case of failure of "weak" opioids, the guidelines recommended using **"strong" opioids**—for example, morphine, hydromorphone, methadone, levorphanol, fentanyl, oxymorphone, and meperidine **(step 3 of the WHO ladder).**
6. These days, the concepts of "strong" and "weak" opioids have been discredited for most clinical situations, and most clinicians would advocate a modified approach to the WHO ladder:
   a. **Start with nonsteroidal antiinflammatory drugs (cyclooxygenase-2 inhibitors might be a choice in selected patients).**
   b. **Add a short-acting opioid on an as-needed basis if needed.**
   c. **Then add a long-acting opioid on a round-the-clock basis if needed.**
   d. **Adjuvant medications should be added whenever indicated.**
7. Medications should be administered on a regular basis, plus on an as-needed basis, which helps build a constant level of the medication in the body, but also addresses exacerbations of pain, which may be provoked by increased activity during treatment.
8. It is worth emphasizing that patients should enter the rung of the ladder appropriate for their presentation. For example, patients presenting with severe and continuous pain should usually be treated with "strong" opioids at the beginning, which may be most effectively administered intravenously in the acute setting. Patients can then be transitioned, once pain is under control, to a regimen consisting of an nonsteroidal anti-inflammatory drug, a sustained-release opioid, plus a short-acting opioid for breakthrough pain.
9. Long-term opioid use may be associated with tolerance and physical dependence; however, neither tolerance nor physical dependence generally reflects aberrant (drug-abusing) behavior. Finally, because of the potential for serious side effects, patients should be monitored and evaluated regularly.

End-of-Life Considerations

Palliative care is the "active, total care offered to a patient with a progressive disease and their family when it is recognized that the illness is no longer curable, in order to concentrate on the quality of life and the alleviation of distressing symptoms within the framework of a coordinated service."

Pain is experienced by the vast majority of cancer patients at the end of life, but it is only one of many symptoms that dying patients may face.[34] Therefore, the need for the availability of comprehensive palliative care and appropriate pain management in a hospital or home hospice cannot be underestimated.

The WHO defines palliative care as "an approach [that] improves the quality of life of patients and their families facing life-threatening illness, through the prevention, assessment, and treatment of pain and other physical, psychosocial, and spiritual problems."

The WHO underscores the principles that palliative care should strive to achieve the following goals:

- Provide relief from pain and other distressing symptoms
- Affirm life and regard dying as a part of the life cycle
- Intend neither to hasten nor postpone death
- Offer a support system to help patients live as actively as possible until death
- Offer a support system to help family members cope during the patient's illness and during their own bereavement, including supporting the needs of children
- Use a team approach to address the needs of patients and their families, including bereavement counseling if indicated
- Enhance the quality of life and may also positively influence the course of a patient's illness

Development of U.S. palliative care consensus guidelines was discussed during a national leadership conference coordinated by the Center to Advance Palliative Care (*http://www.capc.org*) that was held in December 2001 at the New York Academy of Medicine. The end result of this meeting was National Consensus Project, and ultimately

Clinical Practice Guidelines for Quality Palliative Care.[35] In 2003, the American Cancer Society and the National Comprehensive Cancer Network collaborated to produce *Advanced and Palliative Care Guidelines for Patients*.[36] The purpose of these and other guidelines is to build a framework for standardized approaches to patients with end-of-life care that is thoughtful and comprehensive. Ultimately, this led to the development of *Cancer Pain Treatment Guidelines for Patients*,[36] developed in 2005 by the same collaboration (*http://www.cancer.org*).

Patients dying of cancer or other illnesses often experience fear of impending death. Moreover, patients worry about dependents, losing physical control, dying in pain, and physical decline. Clinicians should directly explore patients' fears, ask what their thoughts are about death, support positive coping, address psychosocial and spiritual concerns, and treat ameliorable problems. Treatment for patients dying of cancer may include supportive therapy and, in some cases, pastoral or faith-based counseling. As cancer progresses, patients are often unable to participate in therapy due to limitations in cognition and speech. Thus, it can be helpful for the patient to discuss preferences for treatment early, particularly if there is conflict among family members. Moreover, it may be helpful to encourage patients to plan practical arrangements (e.g., funeral, wills, advance directives).

Patients and their family members may have fears about becoming addicted to pain medications in the end-of-life setting. In addition, some treatment providers may question opioid doses, especially as they are increased and other medications are added. The polypharmacy generally required to treat patients at the end of life increases the probability of drug interactions, particularly in the presence of borderline cognition, cachexia, low intravascular volume, and reduced glomerular filtration.[34] Therefore, patients and their families need education about pain management and reassurance that their loved one will not become addicted. Patients should also be encouraged to express their wishes about future care, including pain medication and possible trade-offs with wakefulness.

Regulatory and legal concerns about prescribing pain medication are present for some physicians in the end-of-life setting. These fears can be

a major barrier to providing appropriate pain management. Fears of sanctions are generally exaggerated. In fact, the opposite problem has occurred multiple times in recent years: successful litigation against a physician for failing to control pain at the end of life. A physician prescribing opioids appropriately for cancer pain is almost never investigated, although due to variability across communities in the United States, local prescribing guidelines should be checked. Documentation of diagnosis and treatment, including the outcomes of opioid treatment, are essential and provide protection in the event of regulatory scrutiny. Read more about regulatory and legal concerns in the "Pharmacologic Options for the Management of Pain" section in Chapter VI.

Delirium is the most common neuropsychiatric complication at the end of life.[34] A clinical approach to treating delirium may begin with screening with the Mini-Mental State Questionnaire to establish the presence of delirium. Delirium is a syndrome with a long differential diagnosis and many treatable causes. Common causes include medications, dehydration, infections, metabolic disorders (e.g., hypercalcemia, hypoglycemia), and brain metastases. The aggressiveness of diagnostic efforts must be appropriate to the clinical situation; clearly, in the setting of impending death, management is symptomatic, as opposed to the more stable situation where quality of life is usually maximized by identifying and treating the cause. Symptomatic treatment of delirium usually consists of high-potency neuroleptics—for example, haloperidol. Although benzodiazepines can be used, they usually worsen the problem in the long-term. Consideration should be given to opioid rotation because accumulation of opioid metabolites can cause delirium. Counseling and education for the patient, family, and staff should also be accomplished.[34]

Preventing toxicity of adjuvant drugs in palliative care is another common challenge in the end-of-life setting. One adjuvant drug at a time should be prescribed in effective, often high, doses. Treatment outcome should be defined before starting treatment, and the adjuvant should be discontinued if deemed ineffective. Sedation and cognition should always be monitored. Finally, opioids should be

used first for pain and should have reached dose-limiting toxicity before prescribing adjuvant medications in the terminal setting.[34]

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VI.

Approaches to the Management of Pain

NONPHARMACOLOGIC OPTIONS FOR THE MANAGEMENT OF PAIN

The biopsychosocial model encompasses biologic, psychological, and social aspects of pain. Nonpharmacologic options for the management of pain can be divided into physical, psychological, and psychosocial dimensions.

Physical Modalities

Therapeutic Exercise

Therapeutic exercise includes the following:

- Range-of-motion exercises
- Stretching
- Strength training
- Cardiovascular conditioning

Range-of-motion exercises can be delivered in a passive, assisted-active, or active manner. Multiple exercise techniques in each of these categories can be used to increase physical functioning. Although exercise is generally limited to range of motion during acute pain,[1] patients should be encouraged to adopt an exercise program as early as possible. Exercise mobilizes joints and strengthens muscles, in addition to enhancing balance and coordination.

Cardiovascular conditioning is also important for maintenance of long-term health.[2] Facilitating exercise is a primary goal of analgesic therapy.

Patients can become discouraged when their pain increases due to therapeutic exercise. Many patients terminate their treatment far too early to achieve maximal benefit. Physicians can choose physical therapists who specialize in treating persons with chronic pain and can encourage them to persist with an exercise program.

Because the primary goal of treatment for individuals with chronic pain is to restore overall functioning, and injuries or disease often diminish physical capacities, the importance of evaluation and treatment with physical measures cannot be underestimated.

Application of Heat and Cold

Early interventions for acute injuries can be rest, ice, compression, and elevation, which can be remembered by the popular mnemonic acronym RICE. These interventions are directed at diminishing swelling and inflammation and are most often effective between 24 and 48 hours after an acute injury.[3]

The application of heat can be made via hot packs, hot water bottles, moist compresses, heating pads, chemical and gel packs, and immersion in water.[4] Cold can also be applied to reduce inflammation via ice packs, towels soaked in cold water, or gel packs.

The use of heat and cold therapies is somewhat controversial for cancer pain because of the risk of increasing tumor growth. Superficial heat is not contraindicated in some recent cancer guidelines.[5,6] However, caution should be exercised for application of deep heat, including by short wave, microwave, and ultrasound.[5] Heat is also contraindicated for acute musculoskeletal injuries because it can result in increases in hemorrhage and edema.[7]

Care should be taken for superficial and deep heat and cold delivery for the following:

- Individuals with insensate tissue
- Cognitively impaired individuals
- Arterial insufficiency
- Bleeding diathesis
- Individuals with metastatic tumors

Physical Manipulations

For acute pain, physical manipulations, such as instructions on repositioning and appropriate ways to rise from bed or a chair, are important in helping the patient reduce movement-related pain early in the course of postoperative pain.

Short-term immobilization of joints or restriction of movement is often necessary to manage painful joints and facilitate healing. Immobilization of joints at angles that approximate the angle of their optimal functioning (e.g., wrist joints at 30 degrees of dorsiflexion) increase functioning when the immobilization is no longer necessary.[1]

For chronic pain, although immobilization can be helpful in the short-term, the benefits are generally outweighed by undesired consequences (e.g., contracture, atrophy, and cardiovascular deconditioning) if used on a long-term basis.[8]

Therapeutic Massage. Massage can be delivered by stroking, kneading, pressing, or rhythmic motions or a combination.[8,9] Massage is also considered to be a complementary medicine technique. Therapeutic massage provides the following:

- A sense of relaxation
- Reduction of muscle tension
- Promotion of circulation
- Improvements in sleep
- Decreased pain[9,10]

Transcutaneous Electrical Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a counter-stimulation technique that is thought to stimulate peripheral nerves directly and alter painful sensations. TENS involves applying low-voltage electrical stimulation to large nerve fibers. Patients report that a "tingling" sensation replaces painful sensations. TENS has been shown to provide effective pain relief in some forms of acute pain conditions, including postoperative pain, oral-facial pain, and pain associated with childbearing.[11] However, the results of research for TENS in chronic pain are mixed.

Some manufacturers of electrical TENS units indicate that TENS over a cancer site is contraindicated. Recent cancer guidelines state that TENS may be beneficial for patients with mild cancer pain.[5,6]

Other physical treatments, including acupuncture, are covered in "Complementary and Alternative Medicine Approaches."

A Word about Functional-Capacity Evaluations. Individuals with chronic pain may be required to provide documentation of the extent of the injury or illness for purposes of work continuation, reassignment, or qualification for disability benefits. The American Medical Association has established a rating system that provides guidelines for quantifying the degree of disability present. However, many conceptual and practical issues are involved in classifying persons with chronic pain conditions.[12] Many physicians treating pain require that qualified professionals complete functional-capacity evaluations when asked to make work-related capacity decisions for individuals with chronic nonmalignant pain.

Psychological Treatments

Some of the psychological treatments used for treating chronic pain are discussed in this section. A combination of psychological and medical treatments is usually more effective than unidimensional treatment for an individual's complex chronic pain problems.

Behavioral Therapies

Operant conditioning or contingency management involves changing the environment for the purpose of modifying behaviors. Behaviors are elicited by stimuli in the environment and are influenced by both their antecedents and consequences. Reinforcement increases behaviors and can be used to change behaviors.

An example of the use of contingency management for a person with chronic pain is observing the attention that is given in response to his or her pain behaviors. If family members pay special attention to the individual when he or she groans or lies down during the day, the person with pain may be inadvertently reinforced to display pain behaviors. As such, pain behaviors and disability tend to increase over time. In this instance, the focus of the response to the patient by individuals in the environment could be changed to giving the patient attention for active engagement, such as performing exercises during the day or going to work.[13]

Contingency management requires careful thought and a plan tailored for the individual. Family members or significant others may need to be involved. Contingency management can be used effectively to help patients increase their exercise and activity level.

Psychophysiologic Techniques

Psychophysiologic techniques, such as relaxation and biofeedback, are directed toward helping the patient become aware of his or her ability to exert some control over physiologic processes of which he or she is not normally aware (e.g., muscle tension, skin temperature, respiration). Biofeedback uses feedback from a device or computer to give information to patients about their progress. Electromyography biofeedback is directed toward relaxing the muscles, which is particularly important in chronic pain conditions. Patients with low back or cervical pain tend to tense muscles around the site of their pain condition, bracing against it. This often causes increased pain due to muscle fatigue.

Biofeedback is also used in myofascial pain and temporomandibular joint syndrome. In addition to alleviating pain from reducing muscle tension, biofeedback can be used to increase peripheral skin temperature, causing dilation of vessels. This process can be helpful in the treatment of some types of headaches.

The outcome of biofeedback research is generally positive, especially when combined with relaxation training. Individuals with migraine and/or tension-type headaches show 50–55% success rates.[14] A review of mind–body therapies found that relaxation and thermal biofeedback are helpful in the management of recurrent migraine.[15] Relaxation and electromyography biofeedback are effective for recurrent tension headache or as a standalone treatment.[15]

Relaxation Techniques

Relaxation techniques are a form of physiologic self-monitoring. Two popular procedures are progressive muscle relaxation and autogenic relaxation. Progressive muscle relaxation is a procedure that involves alternate tensing and relaxing of various muscle groups in sequence. This form of muscle relaxation is often coupled with diaphragmatic breathing and is helpful for patients who are unaware of their level of muscle tension.

Autogenic techniques involve repeating phrases subvocally (e.g., "My right hand feels heavy, warm, and comfortable.") and focusing the patient in a meditative manner as he or she is reclined or sitting quietly in a chair with eyes closed. Guided imagery can be used to focus the patient on changing reactions to his or her painful sensations or to distract from painful experiences. Relaxation differs from hypnosis in that hypnosis involves a suggestion of pain relief and is generally thought to be a more concentrated form of relaxation. Relaxation and imagery have been found to reduce acute pain and procedural pain in patients with cancer pain.[16] Hypnosis is discussed in "Complementary and Alternative Medicine Approaches."

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) combines cognitive techniques with behavioral techniques. Cognitive techniques include changing distorted thoughts, such as "My pain is getting worse and will never get any better." Patients learn to observe their thoughts and how they affect their emotions and subsequent behaviors. Interventions are directed at changing the patient's thoughts to ones that are more realistic and engender positive coping behaviors.

Coping skills training includes identifying the patient's primary ways of coping with pain and changing those skills if they are not in the best interest of the patient's functioning. An example might be changing the patient's wishful thinking (passive coping) to seeking social support, increasing activities, or gaining more information about a problem (active coping).

Behavioral techniques that are commonly used in CBT are the psychophysiologic techniques (e.g., relaxation, imagery) discussed in the previous section and increasing appropriate activity, including pacing, problem solving, and stress management. In addition, maladaptive behaviors are identified and targeted for change.

CBT is an active therapeutic approach in which the therapist helps the patient set goals for treatment and engages the patient in completing homework in between sessions. CBT can help individuals with chronic pain focus and change their reactions to painful sensations, decrease negative emotional responses, and increase functioning. Advantages of CBT include a relatively short time course (usually 6–12 weeks), its evidence-based procedures and demonstrated effectiveness, and its applicability to a variety of pain-related difficulties (e.g., depression, anxiety) encountered by patients with chronic pain conditions. However, because of the active nature of this treatment, it is efficacious only to the extent that patients become active participants.[17]

A review of randomized controlled trials on mind–body therapies for managing pain found multimodal approaches effective. Table 19 includes a summary of some of these studies.

Table 19.
Randomized controlled evidence for multimodal mind–body approaches for pain.

Type of Pain	Evidence for Efficacy
Chronic low back pain[15]	Multimodal approaches combining stress management, coping skills training, cognitive restructuring, and relaxation therapy
Rheumatoid and osteoarthritis[5,15]	Multimodal approaches Cognitive-behavioral therapy, educational/informational approach
Migraine headache[5,15]	Thermal biofeedback, relaxation
Tension headache[5,15]	Electromyography (muscle) biofeedback
Surgical pain (delivered presurgically) [5,15]	Hypnosis, imagery, relaxation
Invasive medical procedure pain[5,15]	Multimodal approaches may be helpful when used as an adjunct
Adult cancer pain[5]	A-level evidence: patient education and hypnosis B-level evidence: cognitive-behavioral coping skills (distraction and cognitive restructuring) Psychotherapy and structured support

Psychosocial Interventions

Family Therapy and Family Interventions. Chronic pain can affect all family members. Family therapy focuses on the family unit and can change the patterns of behavior that are maladaptive. Family therapy should be considered when one or more family members exhibit behaviors that encourage maladaptive coping of the patient, if the family is overwhelmed by other difficulties, or if the patient is a child.[18]

Educational Interventions for Families. Some educational interventions for families have been shown to be helpful especially for families with patients with cancer. One target of such interventions is the patient and family barriers to adequate pain management described by the National Institutes of Health Consensus Statement.[19] These barriers are the following:

- Belief that pain is inevitable in cancer
- Belief that nothing can be done for cancer pain
- Fear of addiction and dependence on opioids
- Fear that drugs will lose their effectiveness
- Fear that reporting pain will exclude the patient from clinical trials or cancer treatments
- Failure to mention pain to providers
- Lack of adherence to treatment regimens
- High cost of medications and treatments
- Cognitive impairment hindering symptom assessment

Decreased pain has been found for cancer patients when education is directed toward alleviating these barriers, compared with those who received standard pain information.[20] Research shows that incongruence in beliefs about pain and pain experience between patients and caregivers results in the following:

- Poorer psychological functioning
- Poorer interpersonal functioning
- Lower quality of life
- Increased anger
- Increased fatigue
- Higher levels of caregiver strain[21]

Coping Skills Training for Couples. Coping skills training generally involves a combination of education, cognitive-behavioral skills, and relaxation training. Keefe et al.[16] trained partners of people with cancer in how to use cognitive behavioral pain-coping skills to assist their loved one toward the end of life. This line of research is

new and quite exciting in that it uses the patient's social milieu to improve pain coping and control.

Couples, Sexuality, and Pain. Couples often experience sexual problems after the onset of pain. Very little research has been conducted in this area. Patients with pain frequently experience the following:

- Decreased libido
- Decreased physical arousal
- Dyspareunia
- Postcoital pain

Pain and physical difficulties because of disability or illness can also impede a couple's usual sexual practices. These problems can affect relationships (e.g., satisfaction, intimacy), as well as identity (e.g., decreased feelings of femininity or masculinity). In addition, some medications used to treat pain or depression can cause sexual dysfunction. Prolonged use of opioids and antidepressants (most notably selective serotonin uptake inhibitors) can cause loss of libido and sexual disturbances in men (e.g., inability to attain or maintain an erection) and women (e.g., infertility, amenorrhea).

In evaluating patients with sexual dysfunction or difficulties, listening and asking questions concerning sexual functioning are significant parts of treatment. Many therapeutic modalities can be used to improve sexual dysfunction, including behavioral therapy, cognitive behavioral therapy, couples therapy, and sex therapy. Importantly, asking about sexual dysfunction can reveal treatable medical causes, such as low testosterone levels in men.

Group Therapy and Support Groups

Different types of therapy can be delivered in groups of 5–10 individuals and can range from coping-skills groups to support groups formed and led by persons with medical conditions. Mental health professionals (psychiatrists, psychologists, or social workers) generally lead therapeutic groups. These groups are usually psychoeduca-

tional or cognitive-behavioral in format and have been shown to be efficacious in increasing coping with chronic pain.

Patient-led support groups vary in effectiveness; some organized support groups provide emotional support and practical suggestions for members; others may focus more on limitations due to pain, dissatisfactions with the medical system, or other reinforcements for pain and dysfunction, all of which may perpetuate disability. In addition, a number of listservs and chat rooms are devoted to persons with various types of medical difficulties, including chronic pain conditions. The accuracy of information obtained from these sites varies, and patients should be critical of information they obtain through these methods.

Spiritual/Religious Support

Faith-based practices are important for many patients as a source of coping, support, and comfort in facing difficult situations and terminal illness. Patients with terminal illness may have existential questions and concerns best answered by a leader of their faith practice. Spiritual and religious beliefs often help patients make sense of their situations and serve as a guide for their future behaviors. Supportive members of faith communities may provide needed social support and/or assistance with tasks of daily living (e.g., grocery shopping). Physicians may not understand the practices or beliefs of a particular patient, and patients may be hesitant to discuss how faith-based support is helpful to them. To the extent that religious and spiritual beliefs and practices can increase the patient's positive coping, facilitation of this process should occur.

Although a large body of research has been conducted on prayer and physical and mental health, few studies have been conducted on prayer and chronic pain. One study investigating the religious and spiritual practices of orthopedic patients with chronic pain found the following:

- Poorer physical health was related to private spiritual practices.
- Pain duration was associated with less forgiveness and less support from a religious or spiritual community.
- Poorer mental health was related to lack of forgiveness, feeling punished and abandoned by God, lack of daily spiritual experi-

ences, little support from a religious community, and not being religious or spiritual.
- Pain, and interference due to pain, were not related to higher levels of religion or spirituality.[22]

Complementary and Alternative Medicine Approaches

The National Center for Complementary and Alternative Medicine, a division of the National Institutes of Health, defines *complementary and alternative medicine* (CAM) as a "group of diverse medical and health care systems, practices and products that are not presently considered to be a part of conventional medicine."[23]

Complementary medicine means that the practice is used *with* conventional medicine, such as music therapy used to soothe a patient after surgery. *Alternative medicine* is defined as practices that are used *instead* of conventional medicine, such as using herbal preparations as a treatment for rheumatoid arthritis instead of drugs recommended by a doctor who practices conventional medicine.[23]

CAM interventions are divided into the following categories by the National Center for Complementary and Alternative Medicine:

- Alternative medical systems (e.g., Ayurveda, traditional Chinese medicine)
- Mind–body interventions (e.g., meditation, prayer)
- Biologically based therapies (e.g., herbal products, vitamins)
- Manipulative and body-based methods (e.g., chiropractic or osteopathic manipulation, massage)
- Energy therapies (e.g., use of electromagnetic fields, biofield therapies such as Reiki and therapeutic touch)

Prevalence of Complementary and Alternative Medicine Practices

Americans are using many forms of CAM, and usage is growing. Consider the following statistics from nationally representative random surveys in 1991 and 1997:

- CAM use increased from 33.8% in 1991 to 42.1% in 1997.
- There was a 47% increase in probability of visiting an alternative medicine practitioner from 1991 to 1997.
- Approximately 38% of users inform their doctors they use CAM.
- Out-of-pocket payments remained similar (64% and 58.3%).
- Visits to CAM practitioners exceeded total visits to U.S. primary care physicians.
- Fifteen million adults took prescription medication with herbal remedies or high-dose vitamins.[24]

CAM was most sought for chronic conditions, including back and neck pain, anxiety, depression and headaches.[24] The following CAM therapies were most used for back and neck pain:

- Chiropractic
- Massage
- Relaxation techniques
- Other practices (yoga, imagery, herbs, energy work)

Mind–Body Interventions

The most studied mind–body interventions are relaxation, meditation, imagery, biofeedback, and hypnosis. Some of these are more studied and integrated into allopathic, or "conventional," medicine. A few of the more common interventions used for pain within the mind–body category are hypnosis and meditation. Massage, relaxation, and biofeedback are discussed in "Physical Manipulations" and "Psychological Treatments."

Hypnosis is a state of deep relaxation that involves selective focusing, receptive concentration, and minimal motor functioning.[25] A National Institutes of Health Technology Panel found strong support for the use of hypnosis for the reduction of pain.[26] Hypnosis has also been shown to do the following:

- Reduce chemotherapy-induced nausea and vomiting[27]
- Improve recovery time after surgery when performed preoperatively[15]

- Improve postsurgical pain[15]
- Improve pain from oral mucositis after bone marrow transplant[28]

There are a variety of meditative practices, many of which derived from Eastern culture or religious practices. Mindfulness-based stress reduction (MBSR) is a modern variant of meditation that has been applied to stress reduction. MBSR purports to change the experience of negative emotions by cultivation of an acute, moment-to-moment awareness of thoughts and feelings. A nonjudgmental attitude toward these thoughts and feelings is learned. This awareness is taught through regular meditative practice. Unlike many other meditative practices, MBSR has been studied for patients with chronic pain[29,30] and cancer.[31]

MBSR has been shown to improve the following:

- Chronic pain[29,30]
- Low back pain[29,30]
- Coping with pain[29,30]
- Stress[32]
- Mood[33]
- Immune system markers in patients with breast and prostate cancer[31]

Mindfulness-based art therapy, a combination of mindfulness practices and art therapy, has been shown to reduce psychological distress and improve the quality of life for patients with breast cancer.[34,35]

Biologically Based Therapies

Herbal Products. Many herbal products purport to relieve pain. A complete review can be found in the Clinical Tools section of http://www.PainEDU.org. Five of the top 10 herbal remedies in the United States are marketed to relieve pain. They are presented in Table 20.[36]

Table 20.
Herbs marketed to relieve pain.

Herb	Uses	Safety/Adverse Reactions
St. John's wort (*Hypericum perforatum*)	Used for depression, anxiety, headache, muscle and nerve pain	Adverse effects: insomnia, anxiety, fatigue, headache. Is probably safe when used appropriately May interact with drugs with serotonin, triptans, opioids, human immunodeficiency virus drugs, digoxin, warfarin, oral contraceptives, chemotherapy, albuterol
Echinacea (*Echinacea purpura*)	Used for migraines, dyspepsia, pain, dizziness, respiratory infection, wound healing	Adverse effects: allergic reaction, nausea, stomach pain, diarrhea, dizziness May interact with acetaminophen, immunosuppressive therapy
Feverfew (*Tanacetum parthenium*)	Used for migraine	Adverse effects: headache, ulcers, gastrointestinal upset May interact with anticoagulants
Ginger (*Zingiber officinale*)	Used for nausea, gastrointestinal upset, thermal burns, topical analgesic	Generally safe when used appropriately. Adverse effects: increased bleeding risk May interact with diabetic drugs, heart drugs, reflux and stomach ulcer drugs
Ginseng (*Panax quinquefolius*)	Used for memory, depression, headache, fatigue	Adverse effects: anxiety, insomnia, headache May interact with other drugs: nonsteroidal antiinflammatory drugs, antipsychotic drugs, hormones, monoamine oxidase inhibitors, immunosuppressants, opioids, alcohol

Herbal preparations are not subjected to the regulatory processes of other drugs, and therefore, a paucity of studies that assess their efficacy and safety exists. There are some well-controlled studies that, on the whole, document the limited efficacy of herbal treatments for pain relief.[36] However, physicians should know what their patients are taking and ask about herbal preparations in a nonjudgmental manner.

Manipulative and Body-Based Methods

Acupuncture. Acupuncture began in China approximately 2,500 years ago. Its primary purpose according to Chinese philosophy is to assess and rebalance the life force of the individual. This life force is known as *qi* (pronounced "chee."). Qi is located on meridians of the body. Stimulation of certain points on the meridians with small-gauge needles rebalances qi in the body.

Western physicians have adopted forms of acupuncture, including pressure applied with the finger (acupressure), with low-frequency electrical current (electroacupuncture), or at points on the ear (auricular).[37–39] More than 1 million Americans are treated with acupuncture every year.[40]

The evidence is considered strong for the efficacy of acupuncture in postoperative pain and chemotherapy nausea and vomiting.[40,41] A metaanalysis found evidence that acupuncture is effective for pain relief for low back pain over sham acupuncture and no additional treatment.[42] Two reviews for cancer patients found the following:

- Pain relief
- Increased mobility
- Reduced cancer treatment–related pain
- Reduced muscle and bladder spasms
- Reduced vascular problems[41,43]

Literature reviews on the efficacy of acupuncture for short-term acute and for chronic pain indicate an overall positive therapeutic benefit, with the caveat that well-controlled studies are

rare and long-term studies are lacking. Empiric studies are difficult to accomplish for a number of reasons, including the absence of standardized treatments for certain conditions. Additionally, many practitioners of acupuncture do not believe the scientific methods of Western medicine are appropriate to study the efficacy of acupuncture.

Drawing on a scientific rationale of trigger point or electrical stimulation therapy, acupuncture is generally recommended for conditions that involve somatic pain. Adverse effects of acupuncture are bleeding and pain at the needle site. It is contraindicated for patients with thrombocytopenia, coagulopathy, or neutropenia.[38] Limitations of acupuncture include the possibility of infection if sterile precautions are not taken. In addition, some practitioners are overzealous about the effects of acupuncture and may promise more relief than is generally expected from any one treatment for acute or chronic pain. Properly practiced, acupuncture is considered safe and is an alternative to conventional symptomatic treatments.[44]

Chiropractic or Osteopathic Manipulative Techniques. Chiropractic or osteopathic manipulation involves movement of the spine. They are used to reduce muscle tension and/or to place the patient's spine in proper alignment.

Limited evidence from systematic reviews supports chiropractic treatment for musculoskeletal conditions.[45] More research needs to be accomplished before these techniques can be recommended for the majority of patients with musculoskeletal pain.

Energy Therapies. Energy therapies involve manipulating the patient's energy to revive the energy flow in the body to enhance health. Energy is generally manipulated without touching the patient (e.g., therapeutic touch). Reiki and Qigong are also techniques in this category.

There is not enough evidence about these therapies to recommend them. However, there are no known risks to these treatments.

PHARMACOLOGIC OPTIONS FOR THE MANAGEMENT OF PAIN

Nonopioid Analgesics

Acetaminophen

Acetaminophen has analgesic and antipyretic properties similar to that of aspirin, without the antiinflammatory effect. Acetaminophen is a common treatment of mild to moderate pain and is often the recommended first-line analgesic therapy for the treatment of osteoarthritic pain.

Its mechanism of action is not well-defined, although it is thought to be associated with the nitric oxide cycle. Acetaminophen *does not* interfere with gastric mucosa protection or platelet aggregation. However, doses in excess of 4 g per day should be avoided in all patients to minimize the risk of rare but potentially serious liver toxicity. Patients with chronic alcoholism and/or severe liver disease can develop hepatotoxicity even at therapeutic doses; therefore, care should be taken when prescribing acetaminophen in these patient populations. Clinicians should also be extremely vigilant when managing warfarin therapy in patients taking acetaminophen, as it can cause potentiation of the anticoagulant effects of warfarin.

Acetylsalicylic Acid

Acetylsalicylic acid, or aspirin, can sometimes be as effective as other nonopioid analgesics in relieving pain. Aspirin is commonly used to treat minor to moderate types of pain, including arthritic conditions, where its antiinflammatory effect (similar to other nonsteroidal antiinflammatories) would be of benefit. Gastrointestinal disturbances (usually upper gastrointestinal) and bleeding due to platelet aggregation inhibition are the most common adverse effects seen with aspirin therapy. Although one of the oldest nonopioid analgesics and considered to be a member of the class of nonsteroidal antiinflammatory medications, the exact mechanism of aspirin is still unknown.

Because of the possible association with Reye's syndrome, aspirin *should be avoided* in children younger than age 12 years with acute viral illness, particularly varicella, or influenza-like conditions. Aspirin should also be avoided by patients with peptic ulcer disease or poor kidney function because this medication can aggravate both conditions. Aspirin is avoided in patients taking blood-thinning medications (anticoagulants) such as warfarin because of an increased risk of bleeding.

Aspirin hypersensitivity may occur and can present with two distinct clinical pictures. In one presentation, the patient develops a respiratory reaction, with rhinitis, asthma, or nasal polyps. In another, smaller subset of patients, anaphylactoid symptoms may occur, such as urticaria, rash, hypotension, and shock within minutes of ingestion.

Nonselective Nonsteroidal Antiinflammatory Drugs

Nonselective nonsteroidal antiinflammatory drugs (NSAIDs) are used primarily for treatment of mild to moderate pain and provide additive analgesia when combined with opioids prescribed for more severe pain conditions or inflammatory pain conditions. NSAIDs work by inhibiting the enzyme cyclooxygenase, which catalyzes the conversion of arachidonic acid to leukotrienes, and prostaglandins, which are known to sensitize nociceptors near the location of the pain.[46] In contrast to opioids, NSAIDs have a distinct ceiling effect for analgesia—that is, increasing the dose beyond a certain threshold does not increase analgesia (but can increase toxicity). NSAIDs do not produce physical or psychological dependence.

NSAIDs are particularly good for bone pain and incident pain, or the type of pain that is provoked by activity (e.g., walking). All types of pain may respond to NSAIDs; however, visceral pain is probably less responsive than somatic pain, and neuropathic pain is often unresponsive.[47]

Although NSAIDs are useful for treating pain, patients should be carefully monitored for adverse effects, including renal impair-

ment, bleeding, gastric ulceration, and hepatic dysfunction. Some less common side effects include confusion, precipitation of cardiac failure, pedal edema, and exacerbation of hypertension.

Extreme caution should be used when prescribing NSAIDs in patients who have any of the following risk factors:

- A history of gastric or duodenal perforation
- Bleeding ulcer
- Concomitant use of anticoagulants (e.g., warfarin, heparin)
- Concomitant use of corticosteroids
- Prior history of long duration of use of NSAID therapy
- Advanced age

The optimal strategy for providing analgesia without gastrointestinal toxicity remains to be determined. Concomitant ulceroprotective treatment—for example, proton pump inhibitors or misoprostol—may be prescribed in high-risk patients. Although nonacetylated salicylates, choline-magnesium-trisalicylate, and salsalate appear not to alter platelet function significantly and are often used in this situation, clinical experience suggests that these medications are not as effective as the NSAIDs at relieving pain.

Cyclooxygenase-2 Inhibitors

Research has shown that there are actually two relevant isoforms of cyclooxygenase, COX-1 and COX-2. COX-1 is present in many tissues, including gastrointestinal tract and platelet, whereas COX-2 is present primarily in inflamed/injured tissue and kidney. Thus, inhibition of COX-2 is likely the primary mechanism of action of NSAIDs, whereas inhibition of COX-1 is the mechanism of some of the major toxicities of NSAIDs: gastrointestinal ulceration and bleeding and platelet dysfunction. Agents that selectively inhibit COX-2 appear to relieve pain and inflammation *without* significant gastrointestinal or platelet disturbance. However, the analgesic efficacy of COX-2 inhibitors has not been proved to be superior to traditional NSAIDs. Indeed, with the current swirl of controversy

surrounding cardiovascular risks that exists today with selective COX-2 inhibitors, these drugs should be used in appropriate patients who either are not at increased risk for complications or in whom typical NSAIDs are not indicated due to risk factors such as those mentioned previously.

Opioid Analgesics

Opioid analgesics are considered to be a mainstay in the treatment of moderate to severe pain that does not respond to nonopioids alone because they are effective, are fairly easy to titrate, and have a favorable risk to benefit ratio. They are often combined with nonopioids because this permits using a lower dose (i.e., opioid dose-sparing effect). Opioids are the first-line approach to moderate to severe cancer-related pain.

Opioids can exhibit their analgesic effects by acting on both peripheral and central mu, kappa, and delta opioid receptors, which inhibits the transmission of nociceptive input from the periphery to the spinal cord, activates the inhibitory pathways that modulate transmission, and alters limbic system activity. Recent research expands the traditional view and shows that opioids may also work peripherally in areas of inflammation. Evidence also bears out that because responsiveness varies in individuals, a patient who has failed with one should be treated with another to investigate greater efficacy. Opioid analgesics are typically classified according to the receptors to which they bind, and are categorized as follows:

- Pure agonists
- Agonist-antagonists
  - Partial agonists
  - Mixed agonist/antagonists
- Pure antagonists
- Other
  - Tramadol

They may also be subdivided further into divisions based on their pharmacokinetic properties:

- Short-acting
- Long-acting

Pure agonists include the following:

- Codeine
- Dihydrocodeine
- Fentanyl
- Hydrocodone
- Hydromorphone
- Levorphanol
- Meperidine
- Morphine
- Methadone
- Oxycodone
- Oxymorphone
- Propoxyphene

These opioids are classified as *pure agonists* because they bind to the mu opioid receptor, do not have a ceiling effect for analgesia, and do not interfere with the effects of other opioids in this class when prescribed simultaneously. Side effects of full agonists include constipation, sedation, nausea and vomiting, mental clouding, addiction, myoclonus, pruritus, sweating, urinary retention, and respiratory depression.

Partial agonists (e.g., buprenorphine) bind with only partial efficacy at the opioid receptor. They have a ceiling effect for analgesia (like NSAIDs) and may produce a withdrawal syndrome when administered to physically dependent patients.

Finally, *mixed agonists/antagonists* include butorphanol, nalbuphine, and pentazocine. Unlike full agonists, these opioids block opioid analgesia at the mu opioid receptor or are neutral at this receptor while simultaneously producing analgesia by activating another opioid receptor (kappa). Agonist/antagonists should not be prescribed with full agonists because doing so could lead to symptoms of withdrawal and increased pain.[8] Although the agonist/antagonists were initially thought not to cause addiction, experience has revealed the opposite. The agonist/antagonists thus have a limited role, if any, in pain management.

Pure antagonists such as naloxone and naltrexone are administered for prevention or reversal of opioid effects.

Tramadol is a useful agent that is unique in that it has a dual mechanism of action. Tramadol acts as a weak agonist at the mu opioid receptor but also inhibits reuptake of norepinephrine and serotonin, like a tricyclic antidepressant. Both properties are necessary for its full analgesic activity. Tramadol is typically used for mild to moderate pain and can be used up to 400 mg per day, given as 25–100 mg every 4–8 hours as needed. Tramadol does not appear to produce tolerance, and although it can be addictive, this is much less common than with the other opioids. Tramadol is *not* an NSAID and does not share the NSAID liabilities of antiplatelet effect and gastrointestinal complications. Because of its tricyclic-like properties, tramadol should be used only with great caution in patients already on these agents. Also, tramadol can precipitate seizures, so it should be used with great caution, if at all, in patients with a history of seizures, brain metastases, or other risk factors for seizures.

Short-Acting and Long-Acting Opioid Preparations

Opioids may be classified according to whether they are short-acting or long-acting. *Short-acting opioids* include codeine, hydrocodone, hydromorphone, oxycodone, meperidine, and fentanyl (available for transmucosal use as a lollipop or buccal tablet). Short-acting agents are characterized by a relatively short onset of action (30–60 minutes) and relatively short duration of action (2–4 hours). Short-acting opioids are used generally for patients with mild to moderate pain, intermittent pain, or breakthrough episodes that are superimposed on constant background pain.

Other opioids may be characterized as *long-acting* by virtue of their intrinsic pharmacokinetic properties (e.g., methadone, levorphanol) or by virtue of their incorporation into a slow-release delivery system (e.g., controlled-release morphine; controlled-release oxycodone; transdermal fentanyl). Long-acting opioids are generally characterized by a slower onset of action, but a relatively long duration, and are therefore used on a round-the-clock basis for patients with constant background pain. Most patients with cancer pain end up on a long-

acting opioid on a fixed-dose schedule for background pain with a short-acting opioid for breakthrough pain. Maximizing the use of long-acting opioids in this setting enhances adherence and affords patients the advantages of more consistent pain relief, increased sleep, decreased episodes of medication taking, and generally improved satisfaction. Although many clinicians have extended this treatment philosophy to individuals with chronic noncancer pain, the long-term advantages and disadvantages of these various approaches to opioid analgesia have not been systematically studied.

Appropriate Dosing of Opioids

An equianalgesic chart should be used when changing from one opioid to another or from one route of administration to another. It is important to remember that the doses listed on equianalgesic charts are just estimates and can vary; the optimal dose for any individual patient is always determined by careful titration and appropriate monitoring. Equianalgesic charts show the oral and intramuscular (IM) doses of opioids that are equivalent to 10 mg of IM morphine. Because few studies exist regarding comparisons between intravenous (IV) doses of different opioids, the American Pain Society[48] recommends that IV doses be based on two assumptions: (1) that half the IV dose will give the same peak effect as a single IM dose and (2) IV infusions or repeated small boluses and IM total dosage will be equal when calculating the 24-hour requirements because IM doses are eventually absorbed.

When a new drug is considered, the equianalgesic chart shows approximate equivalents between the new and old drug. The total dose of each opioid over 24 hours should be recorded, with separate calculations made for parenteral and oral doses of the same opioid if both forms are used. Each 24-hour total should be divided by the equianalgesic dose for that opioid and route, thereby converting the dose into equianalgesic dose units that are each equivalent to 10 mg of IM morphine. The equianalgesic dose units for all drugs should be added. The dose of the new drug can be found by multiplying the sum of the dose units obtained above by the equianalgesic dose for the new drug and route.[48]

The equianalgesic dose conversion charts are derived mainly from single-dose analgesic studies and may not apply to chronic dosing. The American Pain Society Principles of Analgesic Use[48] indicate that dose changes for patients on high doses of opioids can be accomplished in stages by first implementing a partial conversion to minimize the risks of serious miscalculation (withdrawal, severe pain, overdose). For example, a patient with an infusion being changed to an oral preparation might have his or her infusion decreased by 50%, with the remaining 50% of the opioid requirement provided by an oral formulation. Reassessment of this strategy can be made after 24 hours. The half-life of opioids must also be taken into consideration when changing patients to different opioids. Estimates of doses vary widely depending on the half-life of the initial and replacement opioid, sometimes resulting in doses several times the original dose. In cases where the difference between severe pain from underestimating the conversion dose is coupled with safety concerns about overestimating the conversion dose, hospitalization for dose conversion is appropriate.

Routes of Administration of Opioids

The *oral* route of administration should be used first. This route is most convenient and cost-effective. It is a myth that *parenteral* administration of opioids is more effective at relieving pain than *oral* administration. *Effectiveness* (i.e., how well it works) must be distinguished from *potency* (how many milligrams it takes). *Oral* opioids are less potent than *parenteral* opioids—that is, higher doses of *oral* compared with *parenteral* opioids are required to produce the same degree of pain relief because of the first-pass metabolism of opioids in the liver. This has nothing to do with effectiveness—both routes work equally well at *equianalgesic* doses. However, the *parenteral* route*, intramuscular (IM), intravenous (IV)*, and *subcutaneous (SC)*, may be required when the *oral* route is unavailable, rapid titration of opioid dose for severe pain is required, or the *oral* or *transdermal* opioid dose has become so high that only *parenteral* opioids can be conve-

niently administered. Because the ratio of *oral* to *parenteral* equianalgesic dosages differs among opioids, conversion charts are generally necessary when transitioning a patient from one opioid regimen to another. Liquid forms of opioids can be used when patients have trouble swallowing. Also, a number of liquid opioid preparations are fairly well-absorbed *sublingually* and come in various potencies (e.g., morphine, methadone), thus obviating the need for *parenteral* doses in patients who cannot swallow (e.g., esophageal cancer).

Fentanyl lozenges can be used *transmucosally* in patients with breakthrough pain who are unable to swallow or absorb medication. These fentanyl lozenges have the most rapid onset of action of any nonparenteral opioid. A new rapid-onset (15 minutes) short-acting (60 minutes) *buccal* preparation of fentanyl has just received approval for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

When *oral* opioids cannot be delivered secondary to unavailability of the *oral* route (e.g., nausea and vomiting), *rectal* and *transdermal* forms of administration should be considered. *Rectal* administration of opioids is possible but has a relatively slow onset of action and variable pharmacokinetics.[8] The *transdermal* fentanyl patch appears to be a safe and practical alternative to short-acting analgesics in the treatment of cancer pain. The unique pharmacokinetics of the *transdermal* system, including the prolonged time to peak analgesic effect, long elimination half-life, and skin depot concept, should be kept in mind when prescribing the system. A relatively new patient-controlled *transdermal* fentanyl patch is indicated for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization.

IM injections should be avoided as a route of administration of opioid analgesia because of increases in pain that the injection can cause, unreliable absorption, and complications of *IM* shots (e.g., nerve injury, sterile abscesses).[8] In addition, oversedation can occur because of staircased doses given to achieve rapid analgesia. The *SC* route is a useful and underused mode of delivery of both isolated injections and

long-term infusions. *SC* injections can provide rapid relief without the need for *IV* access. *SC* infusions can be used with patient-controlled analgesia pumps for long-term home use; patients can receive a continuous infusion plus boluses as needed. Generally a maximum of 2 ml per hour can be delivered this way; however, both morphine and hydromorphone can be concentrated to as high as 50 mg/ml, which covers nearly all situations. Induration or irritation at the infusion site can be a complication of subcutaneous infusion. *IV* patient-controlled analgesia requires *IV* access but does not have the volume limitations of *subcutaneous* infusions. In addition, opioid analgesia has more rapid onset when given *intravenously* versus *subcutaneously*. When *IV* patient-controlled analgesia is used, approximately 85% of individuals receive good to excellent pain control.[49]

Epidural and intrathecal administration of opioids directly to the spinal axis has gained widespread use because of its efficacy, especially for acute pain that has not responded to less invasive measures. However, side effects, such as pruritus, urinary retention, and delayed respiratory depression, are more common with these routes of administration. Opioids alone do not cause the same degree of hypotension from sympathetic blockade similar to that of local anesthetics because of their action only at opioid receptors, nor do they cause motor blockade that reduces patient mobility.[48] However, opioids are generally used epidurally in combination with local anesthetics, due to the dramatic increase in analgesic efficacy of the combination; also, the combination allows relative reduction of opioid requirements and therefore opioid side effects.

Common Adverse Reactions

Constipation is commonly associated with opioid use, and all patients should receive prophylactic bowel therapy unless contraindicated. Increasing fluids, dietary fiber, exercise, and prophylactic medications may relieve constipation. Prophylaxis for opioid-induced constipation involves stimulants, such as senna derivatives, and stool softeners, such

as docusate. It is important to note that dietary changes are rarely sufficient to counteract the effects of opioids. If constipation develops, the cause and severity of the constipation should be assessed. A clinical history should include the time of the last two bowel movements, stool consistency, stool amount, use of laxatives, and other symptoms, such as nausea and distention.[47] The presence of fecal impaction, hemorrhoids, fissures, or an empty rectum should be established on physical examination. A good bowel movement every 3 days is a reasonable goal of treatment, depending on the patient's baseline.

After beginning an opioid analgesic, many patients complain of *sedation*. Although sedation usually abates in a few days, many patients report persistent sedation. To minimize sedation, administer opioids at the suggested starting doses, with lower doses for elderly or compromised patients, and then increase the opioid dose as necessary. When sedation develops, assess for other causes of sedation, including other sedating medications, sleep deprivation, systemic illness (e.g., hepatic or renal dysfunction), metabolic disturbances, and central nervous system pathology. Reduce the dosage of opioid if pain can be managed at a lower dose, although this is rarely useful because the patient likely uptitrated out of necessity for pain control. If the patient is using a significant dose of the opioid at bedtime to help with sleep, try nonopioid hypnotics (preferably ones with no morning carryover effect) to spare the total opioid burden. Administration of a coanalgesic (e.g., an NSAID) may allow opioid reduction. "Opioid rotation," or changing from one opioid to another, may reduce side effects. Opioid rotation may be necessary due to elimination of toxic opioid metabolites or to patients' idiosyncratic responses to different opioids. Psychostimulant medications are a useful symptomatic treatment for opioid-induced sedation and include caffeine, modafinil (Provigil) (200 mg every day to twice a day), dextroamphetamine (2.5–10 mg by mouth every day or twice a day), and methylphenidate (5–10 mg by mouth every day or twice a day).[48] Stimulant medication generally should not be taken beyond 2 P.M. to avoid interruption of sleep.

Opioids are thought to worsen the performance of psychomotor tasks because of their sedating and mental-clouding effects. As a

result, some safety regulations restrict the use of opioids when driving or using heavy equipment.

A study was conducted to investigate the psychomotor effects of long-term opioid use in 144 patients with low back pain. All subjects were administered two neuropsychological tests (Digit Symbol Substitution Test and Trail Making Test) before being prescribed opioids for pain (oxycodone with acetaminophen or transdermal fentanyl). Tests were then readministered at 90- and 180-day intervals. Test scores significantly improved while subjects were taking opioids for pain, which suggested that long-term use of short- and long-acting opioids does not significantly impair cognitive ability or psychomotor function. This supports the clinical impression that many patients who take opioids for pain over time adjust to the adverse effects of opioids, especially with regard to impaired cognition.[48]

Nausea and vomiting are other common side effects associated with the use of opioids. Although drug-induced nausea is among the most common causes, other causes are possible (e.g., metabolic difficulties such as hypercalcemia or uremia, irritation of the gastrointestinal tract, pharyngeal lesions, brain metastases) and should be ruled out. New onset of nausea or vomiting in a patient who has been on an opioid for over a few weeks is *not* likely related to the opioid. Nausea and vomiting prophylaxis should be instituted in high-risk patients on initiation of opioid therapy. Treatment of nausea and or vomiting should be aggressive if it occurs. To prevent opioid-induced nausea and vomiting in patients at risk, prescribe antiemetics with each opioid dose, at least until the patient's response seems stable and satisfactory. Some common antiemetics prescribed to treat opioid-induced nausea and vomiting are dopamine-blocking agents (e.g., prochlorperazine, 10 mg; haloperidol, 0.5–1 mg; or metoclopramide, 10 mg, before each opioid dose), or 5-hydroxytryptamine 3 (5-HT_3) receptor antagonists (e.g., ondansetron).

Opioids can sometimes cause *dysphoria* or *delirium,* as well as confusion, hallucinations, seizures, restlessness, and bad dreams. Opioid-induced delirium can often be resolved after a reduction of opioid and sometimes switching from one opioid to another. Haloperidol, 0.5–2 mg by mouth every 4–6 hours, or other neuroleptic

agents are effective symptomatic treatments.[8] It is useful to distinguish mental clouding caused by sedation from mental clouding caused by delirium. Psychostimulants may improve these symptoms in the former case but will usually worsen them in the latter.

Some patients develop *pruritus*, which can result from mast cell destabilization by the opioid and subsequent histamine release, or more likely, from central opioid effects on brain or spinal cord. In many cases, the pruritus can be treated with a routine administration of long-acting, nonsedating antihistamines while opioid dosing continues. Although nalbuphine (an opioid agonist/antagonist) or naloxone may be effective, these agents should be used with caution to avoid precipitating withdrawal symptoms. Administration of an agonist/antagonist (i.e., butorphanol) has been shown to be very effective in treating opioid-induced pruritus without affecting analgesic efficacy. Sometimes switching opioids is the most pragmatic strategy for persistent opioid-induced pruritus.

Opioids occasionally cause multifocal *myoclonus*, which consists of sudden unexpected repetitive (but nonrhythmic) jerks of unrelated muscle groups throughout the body. This can be confused with "benign nocturnal myoclonus," a normal phenomenon consisting of a sudden jumping of seemingly the whole body during periods of drowsiness. Multifocal myoclonus is a characteristic feature of the opioid metabolite accumulation syndrome and should prompt concern, as it can progress to seizures. The approach consists of opioid rotation if possible; if not, the myoclonus can be suppressed with a number of agents (baclofen, valproic acid, clonazepam, gabapentin). Any medication that causes increased drowsiness can increase "benign nocturnal myoclonus," which should not arouse concern unless it is part of a progressive neurologic picture.

Urinary retention is sometimes caused by opioids but may be a more frequent problem associated with epidurally administered opioids. Urinary retention can be relieved with bethanechol or in the short-term with opioid antagonists (naloxone, naltrexone, or nalbuphine). It may be necessary to repeat doses to make certain that the bladder is completely empty, and sometimes catheteriza-

tion of the bladder is necessary. Persistent urinary retention that is clearly due to an oral opioid should result in opioid rotation, along with measures to reduce opioid requirements.

Respiratory depression is the most important opioid adverse effect. Opioids typically produce a concentration-dependent shift in the carbon dioxide response curve. When this shift becomes great enough, clinical expression of respiratory depression occurs, usually as a decrease in respiratory rate. Usually with clinically appropriate doses, compensation occurs, and respiratory rate does not decline. Tolerance to the respiratory effects of opioids usually develops quickly, and doses can be increased as necessary without concern. However, in the event of a cardiorespiratory event, a patient's response may be exaggerated due to the presence of opioid concentrations in the bloodstream. The point is that even in the absence of clinical signs, there may still be residual effects on respiratory reserve after tolerance develops, and this must be kept in mind with patients on opioid therapy. In cases where respiration is acutely compromised, the first priorities are, as always, establishing an airway and ventilating the patient. Consider using a dilute solution of naloxone (0.4 mg in 10 mL of saline), administered as 1-mL boluses every minute until the patient is breathing appropriately. Some patients are extremely sensitive to opioid antagonists. There is nothing more distressing to patients, family members, nurses, and physicians than overly aggressive administration of naloxone to a terminal patient resulting in a horrific withdrawal syndrome in the patient's last days or weeks. Patients remember opioid withdrawal forever—it is best avoided. Children and patients who weigh less than 40 kg should have 0.1 mg of naloxone diluted in 10 mL of saline to make a 10 mcg/mL solution, given at 0.5 mcg/kg every 2 minutes.[48a] Naloxone administration should not be given for altered mental status unrelated to opioid overdose.

Prescribing Considerations

Two major considerations are important when prescribing opioids: the *fear of regulatory and legal scrutiny* and the *fear of addiction*, which can ultimately contribute to the undertreatment of pain. Fears of sanctions by

regulatory agencies are largely exaggerated. When prescribing guidelines are followed, investigations by regulatory agencies are unlikely.

Fear of Regulatory Scrutiny. The Federation of State Medical Boards of the United States has recognized the need for the use of opioids in pain management and in 1998 published the *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain*, which appears here:

1. Evaluation of the Patient . A complete medical history and physical examination must be conducted and documented in the medical record. The medical record should document the nature and intensity of the pain, current and past treatments for pain, underlying or coexisting diseases or conditions, the effect of the pain on physical and psychological function, and history of substance abuse. The medical record should also document the presence of one or more recognized medical indications for the use of a controlled substance. Many clinicians use **SOAPP®**, (**S**creener and **O**pioid **A**ssessment for **P**atients with **P**ain), a brief paper and pencil tool, to facilitate assessment and planning for chronic pain patients being considered for long-term opioid treatment.[48b] The tool and accompanying scoring information can be downloaded from http://www.PainEDU.org.

2. Treatment Plan. The written treatment plan should state objectives that will be used to determine treatment success, such as pain relief and improved physical and psychosocial function, and should indicate if any further diagnostic evaluations or other treatments are planned. After treatment begins, the physician should adjust drug therapy to the individual medical needs of each patient. Other treatment modalities or a rehabilitation program may be necessary depending on the etiology of the pain and the extent to which the pain is associated with physical and psychosocial impairment.

3. Informed Consent and Agreement for Treatment. The physician should discuss the risks and benefits of the use of controlled substances with the patient, persons designated by the patient, or the patient's surrogate or guardian if the patient is incompetent. The patient should receive prescriptions from one physician and one

pharmacy where possible. The patient should agree to take medications only as prescribed. If the patient is determined to be at high risk for medication abuse or has a history of substance abuse, the physician may make use of a written agreement between physician and patient outlining patient responsibilities, including (1) urine/serum medication levels screening when requested, (2) number and frequency of all prescription refills, and (3) reasons for which drug therapy may be discontinued (e.g., violation of agreement).

4. Periodic Review. At reasonable intervals based on the individual circumstance of the patient, the physician should review the course of treatment and any new information about the etiology of the pain. Continuation or modification of therapy should depend on the physician's evaluation of progress toward stated treatment objectives such as improvement in patient's pain intensity and improved physical and/or psychosocial function (e.g., ability to work, need of health care resources, activities of daily living, and quality of social life). If treatment goals are not being achieved despite medication adjustments, the physician should reevaluate the appropriateness of continued treatment. The physician should monitor patient compliance with medication use and related treatment plans.

5. Consultation. The physician should be willing to refer the patient as necessary for additional evaluation and treatment to achieve treatment objectives. Special attention should be given to those pain patients who are at risk for misusing their medications and those whose living arrangement pose a risk for medication misuse or diversion. The management of pain in patients with a history of substance abuse or with a comorbid psychiatric disorder may require extra care, monitoring, documentation, and consultation with or referral to an expert in the management of such patients.

6. Medical Records. The physician should keep accurate and complete records to include the following:

- The medical history and physical examination
- Diagnostic, therapeutic, and laboratory results

- Evaluations and consultations
- Treatment objectives
- Discussion of risks and benefits
- Treatments
- Medications (including date, type, dose, and quantity prescribed)
- Instructions and agreements
- Periodic reviews

Records should remain current and be maintained in an accessible manner and readily available for review.

7. Compliance with Controlled Substances Laws and Regulations. To prescribe, dispense, or administer controlled substances, the physician must be licensed in the state and comply with applicable federal and state regulations. Physicians are referred to the *Physicians Manual of the U.S. Drug Enforcement Administration* and *any relevant documents issued by the state medical board* for specific rules governing controlled substances as well as applicable state regulations.

In addition, the Drug Enforcement Agency, along with a number of other agencies, has issued a statement supporting the importance of opioids in the management of pain. Physicians can check these guidelines, as well as others in their communities.

Documentation of the diagnosis, treatment and treatment outcome, as well as periodic review, is essential when prescribing opioids and serves as protection in the event of investigation. An opioid agreement, outlining the expectations of the patient and provider, can be used to document informed consent and the responsibilities of patient and provider. Such agreements often contain stipulations that the physician be the only person to prescribe opioids and that the patient use one pharmacy. These agreements outline appropriate use of opioids, side effect information, and the type of behavior expected from the patient (e.g., no requests for early refills, no changes in doses are made unless the patient has been physically evaluated). They may also define addictive behaviors and indicate the sanctions if the patient engages in these behaviors. Family members and/or significant others may be involved in these conversa-

tions so that they can learn more about the risks and benefits of treatments with opioids. Physicians should review any such agreements with their legal counsel before implementation because such agreements may have legal implications.

Fear of Addiction. Another fear that leads to the undertreatment of pain with opioids is addiction. It is important that the clinician understand, and be able to convey to the patient and family, the distinction between physical dependence, addiction, and pseudoaddiction. *Physical dependence* is a physiologic adaptation that occurs in patients receiving opioid analgesics (as well as other medications, including antiepileptics and certain antihypertensives). Physical dependence is characterized by the development of withdrawal symptoms when a medication is stopped or decreased abruptly and is expected in patients receiving opioid analgesics for more than a few days. Withdrawal can be avoided by tapering the dose when discontinuing treatment.

Addiction, on the other hand, is a chronic neurobiologic disease with genetic, psychosocial, and environmental influences. It is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. *Pseudoaddiction* is a term used to describe behavior that appears to be addictive, "drug-seeking" behavior but is actually an effort to obtain pain relief by a nonaddicted patient who is not receiving adequate analgesia. Additional information on treatment of patients with comorbid substance abuse disorder is found in Ch. VII, in the section "Patients with Substance Abuse Problems." Although primary care practitioners often manage opioids for patients with chronic pain and cancer, they should not hesitate to refer patients to psychiatry, psychology, or pain management centers for consultation and/or evaluation and treatment.

Adjuvant Analgesic Agents

Adjuvant analgesic agents are a miscellaneous group of pain-relieving drugs whose primary indication traditionally is not for the treatment of pain. They are used to provide treatment for specific types of pain,

and at times, to augment the analgesic effect of opioids and/or reduce the side effects of analgesics. Some of the most commonly used adjuvant drugs include corticosteroids, anticonvulsants, antidepressants, local anesthetics, neuroleptic agents, and hydroxyzine.

Corticosteroids. Corticosteroids are often used in palliative care, where they have a number of beneficial effects, including pain reduction, improved appetite, weight gain, antiemetic action, and mood elevation. Steroids are used in the treatment of neuropathic pain due to cord compression, brachial or lumbosacral plexus invasion, or peripheral nerve infiltration. Additionally, they are helpful in treating headache due to increased intracranial pressure, some types of arthritic pain, and pain after visceral obstruction.[47]

Dexamethasone, 12–24 mg/day, and prednisone, 30–100 mg/day, are the most commonly prescribed chronic regimens. Of course, the lowest dose that maintains benefit should be used; often, the best strategy is high initial doses followed by rapid tapering to the minimum effective dose. Beneficial effects of steroids tend to diminish after 2–3 months, and their use is therefore limited to patients with limited time left to live or as a short-term treatment before the institution of other palliative measures.[47] Chronic use of corticosteroids produces weight gain, Cushing's syndrome, proximal myopathy, mental changes, and increased risk of gastrointestinal bleeding.[48] NSAIDs should not, if possible, be used concomitantly with corticosteroids secondary because of risks of gastrointestinal bleeding. Discontinuation of a corticosteroid should be made gradually to minimize the effects of a steroid withdrawal syndrome which may occur due to adrenal suppression.

Anticonvulsants. Anticonvulsants are used for some neuropathic pain conditions to relieve lancinating or stabbing pain.[48] Anticonvulsants have the ability to suppress discharge in pathologically altered neurons, thus inhibiting neural hyperexcitability, which may be responsible for their usefulness in treatment of neuropathic pain conditions.

Gabapentin is a popular treatment choice because it is generally well-tolerated and serious side effects are extremely rare.[47] Gabapen-

tin is indicated for treatment of postherpetic neuralgia but also has been widely studied in treatment of other types of neuropathic pain. Unlike other anticonvulsants, gabapentin rarely causes hematologic or hepatic side effects. Effectiveness studies of gabapentin have shown wide variability in the dose (e.g., 100–3,600 mg) required to produce beneficial results. Consequently, gabapentin should be prescribed in low dosages initially, with titration as needed, and as tolerated.[47] Positive results are usually seen within 2 days, and therefore, upward titration may begin every other day, as needed.[47] Gabapentin is associated with the typical side effects of all central nervous system–acting drugs, including sedation, dizziness, and confusion.

Pregabalin is another anticonvulsant used to treat neuropathic pain. It was approved in 2004 for treatment of diabetic peripheral neuropathy and postherpetic neuralgia.

Other anticonvulsants used to treat pain include carbamazepine and phenytoin; however, the hematologic and hepatic side effects of these drugs have made them less popular than newer agents. Some studies have shown lamotrigine and topiramate useful in the treatment of neuropathic pain, but their higher side effect burden and requirement for prolonged titration have caused them to be a second choice for treatment. Finally, it should be highlighted that opioids are the main treatment choice for cancer pain, even neuropathic cancer pain, unless the pain can be controlled with adjuvants alone.

Antidepressants. Tricyclic antidepressants (TCAs), such as amitriptyline, imipramine, nortriptyline, and desipramine, are useful agents for neuropathic pain, cancer pain, and nonneuropathic pain with certain symptoms (e.g., insomnia, depression, or visceral spasm). Evidence suggests that tricyclic antidepressants suppress pain-signaling through local anesthetic-like effects at sodium channels in neural membranes. They also inhibit reuptake of norepinephrine, serotonin, and dopamine at synapses, which may increase their analgesic effects, as well as improve mood favorably.

Analgesic efficacy is best demonstrated for tricyclic antidepressants such as amitriptyline and nortriptyline, and duloxetine has

recently been approved for the treatment of diabetic peripheral neuropathy, although it is not recommended in patients with a history of hepatic disease.

Common side effects include dry mouth, sedation, urinary retention, constipation, and orthostasis. They may also be associated with cardiovascular side effects, such as increased blood pressure, and conduction blockade. They may also lower seizure threshold. Given that the efficacy of these agents is similar, choice of agent depends on the occurrence of side effects. Dosages for these agents are also comparable and should begin with 10–25 mg by mouth before bedtime and titrate upward as needed.[47] The usual beneficial dose for pain is 50–75 mg before bedtime; however, some patients may require 150 mg/day or more.[47] Although serum levels are not clinically useful for adjusting dosages, they are valuable for monitoring toxicity. It takes 2–4 weeks for analgesic effects to begin.

Topical Analgesics. Topical analgesics are targeted toward a specific area of pain. Typically, topical analgesics (e.g., lidocaine patch, capsaicin) are applied directly onto the painful area. They act locally, so serum drug concentration is insignificant and systemic side effects are unlikely. Titration is not needed, and there are no drug interactions. Topical analgesics are used for both neuropathic and musculoskeletal pain. Capsaicin, derived from the active ingredient in chili peppers, is available over the counter and is widely used. Capsaicin depletes substance P from nerve terminals and is thought through this mechanism to decrease peripheral pain transmission. Clinical trials have reported efficacy in neuropathic pain and focal arthritis and musculoskeletal conditions. These trials could not be adequately blinded (capsaicin stings), however, and the effect sizes seen were similar to those seen in unblinded trials.

NSAIDs are used topically around the world for localized pain; such use is less common in the United States, where these preparations must be custom compounded. However, many positive clinical trials and metaanalyses have confirmed the usefulness and safety

of these preparations, apparently with a fraction of the systemic exposure of systemic NSAID treatment. Examples of such preparations include ibuprofen 5% and ketoprofen 20% cream.

Topical formulations should be differentiated from transdermal formulations, for which the application site is different from the painful region, and systemic effects, including serum drug concentration and possible side effects, can be found. Titration is needed, and drug interactions should be monitored for transdermal formulations.[50]

Several topical local anesthetics are available for use in pain treatment. EMLA® cream is a eutectic mixture of lidocaine and prilocaine and is used to prevent acute procedure-related pain such as that from venipuncture, circumcision, and skin biopsy. EMLA® is available as a cream and as a stick-on anesthetic disk. Although EMLA® is effective at reducing procedural pain, it must be left on for 30–60 minutes under an occlusive dressing before the procedure, which may be inconvenient. ELA-Max® (4% liposomal lidocaine) is another option for topical anesthesia to prevent acute procedural pain. The advantages of ELA-Max® are that it seems to provide clinically relevant anesthesia at 60 minutes, comparable to that produced by EMLA® at 90 minutes, and without requiring an occlusive dressing. These comparisons are based on a small number of generally poorly designed studies.

Once the barrier of intact skin is not an issue, there are a number of topical anesthetic options. Dentists have used benzocaine and other agents effectively for oral anesthesia for generations. Lidocaine 2% jelly is available for coating instruments that are used for urethral or endotracheal intubation and for the topical treatment of urethritis-related pain.

Lidocaine patch 5% is the only topical analgesic approved by the Food and Drug Administration for postherpetic neuralgia. Unlike the topical anesthetics described previously, the lidocaine patch does not produce anesthesia of the affected skin. With chronic use, systemic absorption also seems to be insignificant. The lidocaine patch should be applied directly to the most painful areas. Up to three patches may be used at a time, and they may be trimmed to

conform to the affected area. The recommended dose is to use the patch for 12 hours on and 12 hours off; however, pharmacokinetic data suggest that applying four patches at a time for 18 hours a day was safe. The only significant side effect of the lidocaine patch in some cases has been local skin irritation in some patients.

Neuroleptic Agents. Neuroleptic agents have been used as adjuvant analgesics for many decades; however, their role in the treatment of chronic pain is limited at present. Methotrimeprazine is the only neuroleptic with definite analgesic properties and is occasionally used for patients with opioid tolerance or side effects.[47] Common side effects of neuroleptics include sedation and hypotension. Prolonged use of phenothiazines is associated with tardive dyskinesia.[48] Furthermore, extrapyramidal symptoms can occur, usually in younger patients, and can be treated with diphenhydramine.[48] Other neuroleptics are used for the treatment of anxiety, psychosis, hallucinations, intractable insomnia, nausea, and vomiting.

Anxiolytic/Hypnotic. Hydroxyzine is an antihistamine with anticholinergic (drying) and sedative properties that is used to treat allergic reactions. In addition to its antihistamine effects, hydroxyzine has mild analgesic, antiemetic, anxiolytic, and sedative effects.

Hydroxyzine is usually prescribed at 25–50 mg by mouth or IM every 4–6 hours as needed (0.5–1 mg/kg for children).[48] Although analgesic relief has been demonstrated after IM administration, it is not clear that oral administration produces any analgesic effects.[48] As such, oral administration of hydroxyzine is mainly prescribed to relieve nausea or anxiety.

Adjuvants for Bone Pain. Strontium (a radioisotope) and bisphosphonates are analgesic adjuvants used for metastatic bone pain. Radioisotopes work by delivering radiation to the bone. For example, one study demonstrated that a 10 m curie IV dosage of strontium was an effective adjuvant to local radiotherapy.[48] Although they are effective for the pain of widespread bony metastases, they are complicated by bone marrow suppression.

Bisphosphonates are a class of agents originally used to treat hypercalcemia of malignancy that work by suppressing the process of bone resorption, which seems to be accelerated by malignancy. The most common bisphosphonate used for this indication is pamidronate, which has been shown to reduce skeletal events and pain in patients with metastatic breast cancer and other diseases associated with lytic lesions. Pamidronate is generally well-tolerated and is administered as 90 mg IV in 2 hours every 4 weeks.[48] Another recently introduced agent is zoledronic acid, which has been shown to be effective not only in osteolytic lesions (e.g., breast cancer), but also osteoblastic lesions (e.g.,prostate cancer). The relative roles of these different agents remain to be determined; treatment guidelines are available from the American Society of Clinical Oncology.

RATIONAL POLYPHARMACY AND PAIN MANAGEMENT

The American Society of Anesthesiologists Task Force published the following guidelines in *Anesthesiology* in 2004: "Acute pain management practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management."

Part of these guidelines mentions the idea that "*Whenever possible, anesthesiologists should use multimodal pain management therapy. Unless contraindicated, all patients should receive an around-the-clock regimen of nonsteroidal antiinflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors (COXIBs), or acetaminophen. Dosing regimens should be administered to optimize efficacy while minimizing the risk of adverse events. The choice of medication, dose, route, and duration of therapy should be individualized.*"

Analgesics exert their activity at various sites along the pain pathway. Thus, in theory, multimodal analgesia [i.e., the use of two or more agents with differing mechanisms or multiple modes

of analgesia (e.g., local anesthetics and opioids)] increases the likelihood that pain signals will be interrupted and pain relieved. Research has shown that analgesics with differing mechanisms of action can have additive or synergistic effects through a variety of cellular mechanisms, allowing the use of lower doses of each agent than would be used during monotherapy. A multimodal approach to pain management has long been proposed for treatment of both acute and chronic pain. The World Health Organization, the Agency for Healthcare Research and Quality (formerly the Agency for Health Care Policy and Research), and clinicians endorse the use of more than one agent with different mechanisms of action for the treatment of pain. The goal of multimodal therapy is to increase the efficacy of pain relief with enhanced safety and tolerability.

Below is a diagram by Gottschalk et al. depicting the different sites of action of many of the previously mentioned analgesics, portraying the idea that a multifocal approach could be beneficial.[51]

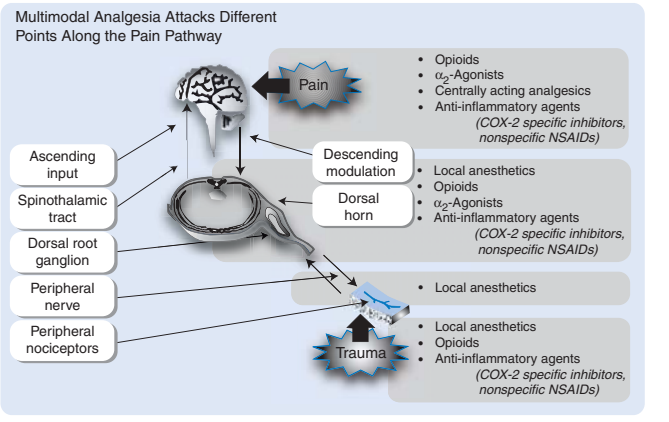

Figure 4.
Multimodal analgesia attacks different points along the pain pathway. Gottschalk A, Smith D. New concepts in acute pain therapy: preemptive analgesia. *Am Fam Phys* 2001;63:1979–1984.

The idea that multimodal therapy, or rational polypharmacy, should be applied toward effective pain management is actually not new. The logic is that to most successfully treat pain, two strategies are beneficial:

1. Attempt to "attack" pain at as many points along the pathway as possible.
2. Minimize the dose of medications with high adverse effect profiles in concert with other medications. This should likely minimize the incidence of adverse effects.

As stated in the previous guidelines for acute pain management, when treating pain, all decisions should be made with respect to the individualized treatment for the patient.

For more information, please refer to the appendixes medication names and dosing information.

INTERVENTIONAL OPTIONS FOR THE MANAGEMENT OF CHRONIC PAIN

The history of the application of interventional techniques in pain management dates back to 1901, when epidural injections for lumbar nerve root compression were reported.[52] Since then, substantial advances have been made in the administration of epidural injections, and many other interventional techniques have been described. Interventional techniques have been distinguished as the favored, and at times decisive, intervention in both the diagnostic and therapeutic management of chronic painful conditions.

Diagnostic and Therapeutic Blocks

Regional anesthesia refers to regional neural blockade for the purpose of blocking or modifying afferent or efferent neural conduction. *Diagnostic,* or *differential, nerve blocks* have been used to determine the source of the pain, differentiate local from central processes, identify

nociceptive pathways, and differentiate between local and referred pain,[53] although there are important limitations to these approaches. For example, a sympathetic nerve block can determine whether the pain is sympathetically maintained, which would guide treatment decisions, but with a high false-positive rate. Diagnostic blocks are sometimes used to decide whether a neuroablative block would be effective, but their predictive value in this regard remains to be demonstrated. Local anesthetics and other agents can be infused via an indwelling catheter in the epidural space or along peripheral nerves to provide analgesia for days to weeks. Local anesthetics with or without steroids can be injected into various structures to provide antiinflammatory effects and pain relief. These techniques are useful in treating pain from joints, bursae, and spinal nerves.

Facet Joint Blocks

The facet joints of the spine can be anesthetized by fluoroscopically guided injections of local anesthetic, either into the target joint or onto the medial branches of the dorsal rami that supply them. The rationale for facet joint blocks is based on the observation that if a particular joint is determined to be the source of pain generation, long-term relief can be sought by directing therapeutic interventions at that joint. In managing low back pain, local anesthetic injection into the facet joints or interruption of the nerve supply to the facet joints has been accepted as the standard for diagnosis of facet joint mediated pain.

Trigger Point Injections

Trigger point injections are probably the most extensively used modality of treatment, not only by interventional pain physicians, but by all providers managing pain. Myofascial pain syndrome is a regional muscle pain disorder accompanied by trigger points. It has been described as a common phenomenon in multiple regions, including the spine. Myofascial trigger points are small, circumscribed, hyperirritable foci in muscles and fascia, often found within a firm or taut band of skeletal

muscle. In contrast, nonmyofascial trigger points may also occur in ligaments, tendons, joint capsule, skin, and periosteum. Trigger points assist in the proper diagnosis of myofascial pain syndrome.

Neurolysis

Neurolytic agents (alcohol, phenol, and glycerol) injected around the nerve produces destructive changes in the nerve to decrease pain transmission. Other techniques to alter functioning of nerves include cryotherapy (cold) and radiofrequency (heat) lesions. Although these techniques can result in significant pain relief, complete destruction of the nerve can be accomplished only with surgical resection.[54] Neurolysis of the visceral ganglia can be used for visceral pain associated with cancer. Neurolytic techniques are also used to treat neuropathic pain. Neurolytic nerve blocks are generally reserved for intractable pain in the cancer setting, due to their inherent risks and the high rate of pain recurrence. Extreme consideration must be made when selecting patients for this technique, as it is ablative in nature and irreversible.

Interventional Techniques

Sympathetic blocks using regional anesthetic techniques and radiofrequency thermoneurolysis or neuromodulation with spinal cord stimulation or peripheral nerve stimulation are often management options for reflex sympathetic dystrophy, and causalgia, also known as *complex regional pain syndrome* (CRPS) types I and II. Radiofrequency neurolysis is really an extension of a continuous regional sympathetic block or neurolytic block, providing long-term relief with added safety. Consideration of sympathetic blocks is to facilitate management of complex regional pain syndrome with analgesia commensurate with a program of functional restoration and sympatholysis to provide unequivocal evidence of sympathetically maintained pain. Once it is established that sympatholysis is effective, it is important to repeat the procedure to determine whether an increasing duration of effect can be expected in any particular patient. If this

is the case, these individual blocks may be all that are necessary to enable a patient to regain function. When sympatholysis completely relieves the symptoms and facilitates exercise therapy but is limited to its duration of effect, it is appropriate to consider a prolonged block using radiofrequency neurolysis. Radiofrequency has been described for lesioning of the cervical sympathetic chain, thoracic sympathetic chain, and lumbar sympathetic chain; in cases of complex regional pain syndrome I and II; as well as for neuropathic pain.

Implantable Technologies

Spinal cord stimulation and peripheral nerve stimulation are techniques that involve electrical stimulation of the spinal cord or peripheral nerves via an implanted pulse generator that delivers electrical signals to these structures. In the United States, the primary indications for spinal cord stimulation are failed back surgery syndrome. Patients experience a "buzzing" feeling that is associated with reduced pain intensity. These signals are thought to stimulate large afferent fibers and inhibit the noxious signals mediated by A delta and C-fibers.[55] Spinal cord or peripheral nerve stimulation appears to be most effective for individuals with chronic neuropathic pain, peripheral vascular disease, or chronic angina.

Implantable intrathecal pumps can deliver a continuous infusion of analgesic medications (e.g., morphine) directly to the spinal cord. Implantable pumps can be useful in the management of cancer pain or intractable chronic pain of noncancer origin. For a few patients, they may be used when the side effects of oral opioids are intolerable. Proper patient selection, as with all forms of pain management strategies, is critical for the success of implantable technologies.

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VII.

Pain Management in Special Patient Populations

INFANTS AND CHILDREN

The myth that pediatric patients do not experience the same degree of pain as adults do was routinely taught to clinicians in training until fairly recently. The foundation of faulty logic was that infants and children had nervous systems that were not yet fully developed, and do not retain memories of their earlier years. Actually, recent animal studies show the opposite is true and that due to a stronger inflammatory response, along with decreased central inhibition, infants and children most likely deal with a higher level of pain than adults do. Indeed, it may be purely the lack of the ability to appropriately communicate the severity of pain that results in undertreatment of pain in this patient population.

Assessment of pain in this special population can be challenging, but *is* possible. Indeed, observational tools as well as physiologic parameters such as heart rate, respiratory rate, and oxygen saturation have been shown to be valid means to assess the degree of pain that a child is feeling.

Tables 21 and 22 are two examples of the commonly used validated observational tools for assessment of pain in infants and children.

Table 21.
CRIES Neonatal Postoperative Pain Scale[1]

	0	1	2
Crying	No	High-pitch, consolable	Inconsolable
Required FiO_2 to maintain SaO_2 at least 95%	No	<30%	>30%
Increased heart rate and blood pressure	No	11–20% increased	>20% increased
Expression	Calm	Grimace	Grimace and grunt
Sleepless	No	Frequent awakening	Constantly awake

Scores are added up to an assessment range of a 0–10 pain level.

Table 22.
Face, Legs, Activity, Cry, and Consolability Scale[2]

	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints

(continued)

Table 22.
Face, Legs, Activity, Cry, and Consolability Scale[2] (Continued)

	0	1	2
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

Scores are added up to an assessment range of a 0–10 pain level.

Management of pain in the pediatric population should occur within a relationship among the treatment team, the child, and his or her parents or guardians. The parents or guardians usually end up being the single most important and passionate advocate for aggressive pain management in infants and children.

Effective treatment usually combines pharmacologic and nonpharmacologic interventions.

Nonpharmacologic interventions include several psychological techniques such as imagery and relaxation training. Moreover, some practical techniques include minimizing unnecessary procedures and discussing procedures in an age-appropriate manner.

With respect to pharmacologic treatments, the medications used to treat pain in infants and children are similar to those used in adults. However, some special considerations are important. Aspirin and its derivatives should be avoided in patients with pain coexisting with any kind of viral syndrome-like symptoms who are younger than age of 19 unless specifically indicated, due to the incidence of Reye's syndrome. Most analgesics and local anesthetics are metabolized through the liver, and in the first 6 months of life, the liver may be relatively immature and require dosage adjustments of medications to compensate for this immaturity. Newborn infants usually have a decreased glomerular filtration rate in the first week of life. Newborn infants also have a relatively higher percentage of body weight that is water, resulting in an increased volume of distribution.

Treatment interventions for children with cancer pain include analgesics, adjuvants, regional analgesia, chemotherapy, and radiation therapy. It is important to note that most medications have not been tested in children, and therefore, prescribing medications to children should follow the World Health Organization approach. Acetaminophen is relatively safe for relief of mild pain, and can be administered orally or rectally.[3] Nonsteroidal antiinflammatory drugs (NSAIDs) are not recommended for patients with cancer who also suffer from thrombocytopenia. When pain is moderate to severe, opioid analgesics are effective and should be administered orally whenever possible. Children should be administered "rescue" doses, particularly if they are receiving continuous infusion. Regular monitoring of side effects is important given that children are often unable to communicate side effects that they may be experiencing (e.g., pruritus, constipation).

The following table provides a good set of basic principles that should routinely be considered when treating and assessing pain in infants and children.

Table 23.
Basic Principles of Pain Management in Infants and Children

Neuroanatomic components and neuroendocrine systems are sufficiently developed to allow transmission of painful stimuli in the neonate and child.
Pain in newborns and children is often unrecognized and undertreated. Neonates *do* feel pain, and analgesia should be prescribed when indicated during medical care.
If a procedure is painful in adults, it should be considered painful in newborns, *even if they are preterm.*
Compared with older age groups, infants and children may experience a greater sensitivity to pain and are more susceptible to the long-term effects of painful stimulation.

(continued)

Table 23.
Basic Principles of Pain Management in Infants and Children (Continued)

Adequate treatment of pain may be associated with decreased clinical complications and decreased mortality.
Sedation does not provide pain relief and may mask the child's response to pain.
A lack of behavioral responses (including crying and movement) does not necessarily indicate a lack of pain.
Severity of pain and the effects of analgesia can be assessed in the pediatric patient. Health care professionals have the responsibility for providing a systematic approach to pain management, including assessment, prevention, and treatment of pain in this patient population.
Treatment should include the appropriate use of environmental, behavioral, and pharmacologic interventions.
Environment should be as conducive as possible to the well-being of the child and family.
Education and validation of competency in pain assessment and management for all clinicians are a professional responsibility and very important when it comes to caring for pediatric and adult patients.

Adapted from The National Pain Management Guideline. Agency for Health Care Policy and Research. *Management of postoperative and procedural pain in infants, children, and adolescents*. 1992. Publication No. 92-0032. Available at http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat6.chapter8991. Accessed August 2, 2007.

ELDERLY PATIENTS

Elderly patients with pain are another group of patients who are often understudied and undertreated. Despite the fact that the prevalence of pain increases with age, the use of analgesic medication declines.[4] The reasons for the undertreatment are due to human error. Some include the following:

- Underreporting of pain by patients due to accepting it as a consequence of aging
- Sensory impairments might hinder the patient's ability to communicate the degree and source of pain
- Public and clinician attitudes about aging and pain influence tendencies to treat
- Long-term care facilities consist of staff that may be less educated about pain management than those working in acute care facilities
- Cognitive impairment can interfere with the elderly patients' ability to complete pain assessment instruments and adhere to a prescribed treatment regimen
- Reluctance to prescribe opioids due to adverse effects, such as confusion or delirium

All elderly patients should be considered at increased risk for undertreatment of pain. Assessment of function is critical in assessing pain in elderly patients. The ability to perform activities of daily living is of paramount importance in elderly patients, as they may be solely responsible for their own care or the care of a spouse. Because depression and signs of chronic pain may frequently coexist, elderly patients may exhibit decreased socialization, which may go unrecognized, and they may further suffer from the inability to care for themselves.

The likelihood is that pain in elderly patients stems from one of three causes. First, there is the likelihood that it is as a result of a coexisting medical illness. Second is the likelihood of a result of aging, such as spinal stenosis or osteoarthritis. Finally, there is the likelihood that it is a part of a neuropsychiatric disorder. Of course, there may be overlap, but this categorization usually helps to establish the best course of treatment. The treatment must obviously try to address the specifics of the causes.

Treatments for elderly patients with mild to moderate pain include acetaminophen and NSAIDs. Acetaminophen is considered effective and safe. NSAIDs can cause increased risk of gastric and renal toxicity, cognitive impairment, constipation, and headache.

Opioids are often used to treat pain in elderly patients. Although opioids have been traditionally viewed as more risky than nonopioid "adjuvant" analgesics, such as tricyclic antidepressants or anticonvulsants, the truth may actually be exactly the opposite. Addiction and tolerance with opioids seem, from clinical experience, to be significantly less of a problem in the elderly, whereas the risks of the adjuvant agents, such as mental status changes and falling, appear to be greater. Thus, the risk to benefit ratio may favor opioids over other agents in the elderly. Of course, this remains a controversial issue. Due to differences in metabolism, some older patients appear to be more likely to experience opioid side effects such as cognitive and neuropsychiatric dysfunction than younger patients. Therefore, a slow titration schedule beginning with minimal doses might be preferable to more aggressive titration as in a younger patient.

Similarly, interventional treatment, such as spinal cord stimulation and intrathecal analgesia, although often perceived as invasive and risky, may actually be safer than long-term pharmacologic approaches for some elderly patients. Other treatment options include cognitive-behavioral therapy, physical therapy, and multidisciplinary treatment. Aggressive rehabilitation is particularly important in the elderly, who are particularly prone to rapid deconditioning and whose ability to function depends on fine degrees of conditioning. Clinicians should be careful not to undertreat pain in the elderly; approach the treatment of pain in this population with patience and balance.

PREGNANT AND LACTATING PATIENTS

When possible, the use of nonpharmacologic treatments should be maximized for noncancer pain in pregnancy. These include judicious rest, pacing, various harnesses designed for pregnancy, ice and heat, and other physical therapy modalities. In general, NSAIDs are avoided. Acetaminophen is generally considered safe in clinical practice. Despite a dearth of data, opioids are widely used for severe pain during pregnancy and are considered relatively safe.

It is important to consider consulting with the obstetrician-gynecologist of record before administering pain medications to pregnant or lactating patients when questions exist with regard to safety.

The Food and Drug Administration has created a categorization of drugs based on empirical findings and safety for use in pregnancy[5]:

Category A

Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.

Category B

Animal studies have revealed no harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women.

Or

Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.

Or

No animal studies have been conducted, and there are no adequate and well-controlled studies in pregnant women.

Category C

Animal studies have shown an adverse effect, and there are no adequate and well-controlled studies in pregnant women.

Category D

Studies in animals or pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.

Category X

Studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

There are many problems with the current system of drug labeling and categories in pregnancy, however. There are very few drugs

in category A and very few drugs in category X. In fact, 70% of drugs are category C, but not all category C drugs have the same level of risk. New pregnancy labeling soon to be implemented by the Food and Drug Administration will include summary of risk assessment, clinical considerations, and data, and, it is hoped, provide more detailed guidelines for safe use of medications in this special patient population.

TERMINALLY ILL PATIENTS

Please refer to Chap. V for information about end-of-life care and palliative care guidelines.

COGNITIVELY IMPAIRED PATIENTS

As mentioned previously, pain is a common phenomenon in the elderly patient population because the likelihood of these patients suffering from conditions such as cancer and arthritis problems is increased. Cognitive impairment is another condition with increased incidence in this patient population. Undertreatment of pain in this patient population is only compounded by the coexistence of cognitive impairment. Indeed, cognitive impairment may be responsible for preventing one of the single most important signs needed to treat pain—the ability to communicate suffering. This can make the accurate assessment of pain in those with severe cognitive impairment one of the most significant challenges in the field of pain management.[6] This also makes information available from family and caregivers invaluable.

Pain management in the absence of a detailed history can prove quite challenging. Although caregiver information is critical, it may be incomplete due to the lack of exhibition of normal pain behavior. Sometimes, the signs that cognitively impaired patients exhibit are

not discrete or obvious, but may be the only clues available, including the following:

- Changes in body posture
- Grimacing
- Decreased willingness to participate in activities that would normally be engaging
- Somnolence due to exhaustion
- Increased nonspecific vocalization
- Agitation
- Crying
- Resistance to physical contact
- Resistance to ambulation

To successfully approach pain assessment and management in the cognitively impaired patient, the practitioner should realize that the most accurate data for assessing pain are obtained in the following order:

1. Patient's report of pain
2. Reports of patient's pain by family or friends or other caregiver
3. Patient's behaviors
4. Physiologic parameters (most useful in acute pain)[7]

A possible recent event that is the cause of the pain (e.g., recent fall) should be included in the investigation.

Clinicians should avoid relying on their own subjective judgment to estimate the degree of a patient's pain. Efforts should be directed toward seeing if a patient can use some form of self-report. This requires that the patient be able to communicate the existence of pain through vocal or nonvocal communication and to rate the intensity of the pain. Several studies have demonstrated that elderly patients with mild to moderate cognitive impairment can respond fairly reliably to measures of pain intensity.[8–10]

The following steps recommended by the *Consensus Statement from the Veteran's Health Administration National Pain Management Strategy*

Coordinating Committee are quite valuable in helping to try to assess and treat pain in the cognitively impaired patient:

- Observation of behaviors to assess pain
  - When a patient is unable to use a self-report method despite efforts toward education, assessment must rely on observation of behaviors. Family members or consistent caregivers can provide valuable insight into the patient's usual behaviors and changes in behaviors that might indicate the presence of pain.[11]
  - Some common pain behaviors in cognitively impaired older persons have been identified.[11,12] These include signs mentioned previously. However, some patients with cognitive impairment exhibit little or no specific behaviors associated with pain. These pain behaviors have not been systematically evaluated in younger patients with cognitive impairments.
  - Pain behaviors should be observed and assessed both at rest and during movement.[9,13–15] Weiner and Herr[6] and others have noted that it is important to consider other causes of behaviors when relying on observation to assess pain. It is important to consider these other potential causes of distress behavior so that analgesic treatment does not mask problems such as infections, constipation, bladder problems, and primary mood disorders.
- Empirical trials of analgesics
  - Empirical trials of analgesic medication can be used as part of a pain assessment. This should be done in conjunction with other methods of assessment to evaluate the hypothesis that the behaviors are indicative of significant pain.[16,17] This should not be a first-line method of assessment. There are no tested protocols for this practice. It is very important to consider other potential causes of distress behaviors or agitation that could be masked or worsened by analgesics. Many analgesics can negatively alter cognitive status, and this should be considered during the course of a trial.

Changes in function and activity as well as other pain behaviors should always be assessed in the context of an analgesic trial.

- Tools for assessment of pain in cognitively impaired patients
  - A number of devices and protocols have been developed to aid in the assessment of patients who have impaired communication due to failures in cognition. These devices are based on observation of behaviors. Most of the available instruments have been developed for use with elderly patients. All the tools currently available suffer from a lack of studies to determine adequate reliability and validity. Clinicians should be very cautious about using an instrument that does not have established reliability and validity even if it appears to have face value.[11]

A comprehensive review of currently published tools for assessing pain in nonverbal persons with dementia is available at The City of Hope Web site (http://www.cityofhope.org),[18] as listed below:

- Abbey Pain Scale[19]
- Assessment of Discomfort in Dementia[20]
- Checklist of Nonverbal Pain Indicators[13]
- Discomfort Scale-Dementia of the Alzheimer's Type[21]
- Doloplus 2[22]
- Face, Legs, Activity, Cry, and Consolability Pain Assessment Tool
- Nursing Assistant-Administered Instrument to Assess Pain in Demented Individuals[23]
- Pain Assessment in Advanced Dementia Scale[24]
- Pain Assessment for the Dementing Elderly[25]
- Pain Assessment Scale for Seniors with Severe Dementia[26]

Although successful treatment of pain in the cognitively impaired patient remains challenging, it is the clinician's responsibility to use all possible means available to successfully manage this difficult condition.

PATIENTS WITH SUBSTANCE-ABUSE PROBLEMS

The risk of inadequately managing pain increases with patients with addictive disorders or substance abuse problems. It can be helpful to use objective screening and management tools such as the **SOAPP®**[27] (**S**creener and **O**pioid **A**ssessment for **P**atients with **P**ain) and **COMM™**[28] (**C**urrent **O**pioid **M**isuse **M**easure), which can be downloaded from http://www.PainEDU.org.

Many factors are responsible for this undertreatment:

- Inadequate clinician training in pain management and addiction medicine
- Lack of acknowledged differences between dependence, addiction, and tolerance
- Fear of contributing to addictive behavior by using opioids
- Societal prejudices on patients with addictive disorders
- Fear of regulatory penalization.

Challenges in treating pain in this patient population are compounded by the patient's perception that the pain they experience is a major cause of their addictive behavior and also an obstacle to withdrawal of the offending agent. Patients with addictive disorders sometimes have problems managing opioids by themselves, and this may indeed lead them to be deprived of a potentially valuable component of their pain treatment.

A joint statement from 21 health organizations and the Drug Enforcement Administration released in 2001 titled Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act *states the following important points with respect to pain management in patients with substance abuse problems:*

> "As representatives of the health care community and law enforcement, we are working together to prevent abuse of prescription pain medications while ensuring that they remain available for patients in need.
>
> Both health care professionals, and law enforcement and regulatory personnel, share a responsibility for

> ensuring that prescription pain medications are available to the patients who need them and for preventing these drugs from becoming a source of harm or abuse. We all must ensure that accurate information about both the legitimate use and the abuse of prescription pain medications is made available. The roles of both health professionals and law enforcement personnel in maintaining this essential balance between patient care and diversion prevention are critical.
>
> Preventing drug abuse is an important societal goal, but there is consensus, by law enforcement agencies, health care practitioners, and patient advocates alike, that it should not hinder patients' ability to receive the care they need and deserve."

This consensus statement is necessary based on the following facts:

- Undertreatment of pain is a serious problem in the United States, including pain among patients with chronic conditions and those who are critically ill or near death. Effective pain management is an integral and important aspect of quality medical care, and pain should be treated aggressively.
- For many patients, opioid analgesics, when used as recommended by established pain management guidelines, are the most effective way to treat their pain and often the only treatment option that provides significant relief.
- Because opioids are one of several types of controlled substances that have potential for abuse, they are carefully regulated by the Drug Enforcement Administration and other state agencies. For example, a physician must be licensed by state medical authorities and registered with the Drug Enforcement Administration before prescribing a controlled substance.
- In spite of regulatory controls, drug abusers obtain these and other prescription medications by diverting them from legitimate channels in several ways, including fraud, theft, and forged prescriptions and via unscrupulous health professionals.

- Drug abuse is a serious problem. Those who legally manufacture, distribute, prescribe, and dispense controlled substances must be mindful of and have respect for their inherent abuse potential. Focusing only on the abuse potential of a drug, however, could erroneously lead to the conclusion that these medications should be avoided when medically indicated, generating a sense of fear rather than respect for their legitimate properties.
- Helping doctors, nurses, pharmacists, other health care professionals, law enforcement personnel, and the general public become more aware of both the use and abuse of pain medications enable all clinicians to make proper and wise decisions regarding the treatment of pain.

Below is a table with some basic principles and strategies for using opioids in the patient with a known substance abuse problem. Never forget that consultation with a specialist in pain management may always be a valuable choice in management of difficult patient populations.

Table 24.
Strategies of Opioid Use in the Patient with Known History of Substance Abuse

Support the individual to help achieve and sustain recovery from addiction.
Provide medications in manageable amounts to patients.
Use schedules and dosages that are less likely to cause euphoric effects, but retain efficacy.
Require a written agreement between you and the patient with respect to abuse of prescribed medications.
Communicate as appropriately necessary with significant others.
See patient frequently to assess for signs and symptoms of abuse.
If there are signs of medication abuse, obtain frequent urine screens, schedule frequent clinic visits, and encourage substance abuse counseling.
If safety concerns outweigh the potential of treatment, discontinue opioid therapy, and use nonopioid approaches.

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VIII.

Patient Level Opioid Risk Management

RISKS OF OPIOID THERAPY

Chronic pain is a major public health problem in the United States, and opioids, for better or worse, remain an essential tool in the armamentarium against acute and chronic pain. Owing to substantial efforts to improve awareness and treatment of chronic pain, the availability of opioids has increased dramatically in the past several decades. Although much more remains to be done to ensure appropriate access to opioids, opioid prescribing is currently at the highest level in decades, allowing patients with cancer and noncancer pain unprecedented access to these analgesics.

Opioids, like all medications, are associated with risks, and the prevalence of negative consequences of opioid use has risen concomitantly with their increased use. The risks of greatest concern have been *abuse* and *addiction*. Prescription opioid abuse is rising faster than any other type of drug abuse and is now second only to marijuana in terms of prevalence of abuse and addiction, and ahead of cocaine and heroin by many measures. Current projections suggest that approximately 1.5 million Americans meet criteria for abuse or addiction to prescription opioids, which is nearly 1% of the population. Although some clinicians have been comforted by a mythology that addiction does not occur in "legitimate" pain patients, the reality is that there is significant overlap between patients with pain and those with addictive disorders; because the prevalence of chronic pain and of addiction is so high, no clinician is

free from treating patients with comorbid pain and addiction. This becomes clear when one considers that the background rate of active substance abuse is approximately 10% in the general U.S. population; that substance abuse increases the risk for certain types of pain; that 20–40% of pain patients on opioids have substance abuse problems; and that pain is the number one reason patients see doctors. The presence of comorbid addiction significantly complicates the treatment of pain, and the presence of comorbid pain significantly complicates the treatment of addiction.

A unique feature of prescription drug abuse as a complication of medical prescribing is that the problem occurs not only in patients, but also in their families and the community. Because one of the major sources of abused prescription opioids is the prescriptions of friends and family, it is clear that many of the patients to whom clinicians prescribe are the source of medications that put their family and the community at risk, either from intentional diversion by the patient or by theft or other unintentional pathways to diversion. The prescriber therefore has unique obligations to prescribe opioids in a manner that minimizes potential harm to nonpatient collaterals.

Side effects, such as nausea, vomiting, dizziness, sweating, and constipation, are commonly experienced risks of opioid therapy that can to a great extent be prevented or treated. Another risk of opioid therapy, which has not been widely publicized although observed for centuries, is endocrine disturbance, particularly testosterone deficiency.

REGULATION OF OPIOIDS

The use of opioid analgesics in the United States is governed by a combination of policies at federal and state levels. The Food and Drug Administration approves medications as safe and effective for medical use. After a drug has been approved, a licensed physician can prescribe the medication for any purpose he or she sees fit, whether or not it is described in the product label, as long as it is

consistent with community standards of good medical practice. Opioid analgesics are also subject to laws governed by the Controlled Substances Act of 1970 and enforced by the Drug Enforcement Administration. According to the legislation, drugs with abuse potential are assigned to one of five categories, with progressively higher categories associated with increased abuse liability. Schedule I includes drugs with no officially recognized medicinal value in the United States, such as lysergic acid diethylamide (LSD) and marijuana. Most opioid analgesics fall into the Schedule II [e.g., oxycodone (Oxycontin), oxycodone and acetaminophen (Percocet), fentanyl] or Schedule III [e.g., hydrocodone (Vicodin), codeine with acetaminophen, buprenorphine] category.

All clinicians must be familiar with the rules regarding controlled-substance prescribing in their states. Such regulations control activities such as calling in prescriptions, writing refills, calling in emergency supplies, and so forth. Prescribing opioids to patients with pain in the course of usual medical practice, and in the context of a legitimate doctor–patient relationship, is permitted. Moreover, the courts increasingly expect clinicians to attend to patients' pain issues, including if this requires the use of opioid analgesics. It is rare for physicians acting in the context of appropriate medical practice, and maintaining adequate records, to be censured for prescribing opioids to patients with pain.

One common source of confusion is whether physicians can prescribe to patients with addiction. The simple answer is that physicians with current licenses and Drug Enforcement Administration registrations can prescribe opioids, including methadone or buprenorphine, to patients with pain, whether or not the patient has an addictive disorder (although this may not always be advisable). To prescribe for the "maintenance treatment" of addiction, a physician must have a special license or waiver to prescribe maintenance treatment, whether or not the patient has pain. Of course, in the patient with comorbid pain and addiction, it may not be clear under which regulation the medication is prescribed to treat pain or the addiction. Nonetheless, physicians must be mindful of the applica-

ble regulations. Unless specially licensed, physicians must be prescribing for pain, not addiction, even in patients with comorbid addictive disorders, and the medical chart must reflect this practice.

OPIOID RISK MINIMIZATION IN CLINICAL PRACTICE

Although there are no validated guidelines for the use of opioids in chronic pain, the following are a reasonable set of considerations and recommendations consistent with current thinking in the field.

The prescribing of opioids for the treatment of pain is no different than the prescribing of any medication for any disorder. As in the example of insulin treatment for diabetes, all therapies have complications, which are more likely to occur (by definition) in high-risk patients. Therefore, patients should be screened for risk level on initiation of therapy and reassessed periodically. **SOAPP®** (**S**creener and **O**pioid **A**ssessment for **P**atients with **P**ain), to be used when considering initiating opioid treatment, and **COMM™** (**C**urrent **O**pioid **M**isuse **M**easure) a follow-up tool for patients who are prescribed opioids, can be downloaded from http://www.PainEDU.org.

If indicated, opioid therapy can be initiated on a trial basis, and the trial can continue for as long as the patient is on treatment. In general, a trial period of 3 months can be recommended. At each follow-up visit, with a tool such as COMM™, the patient goes through a semistructured assessment that assesses key outcome variables, but that need not be excessively time-consuming if approached systematically. Based on the assessment, there are five options for how to handle the opioid therapy:

1. Continue it without change.
2. Adjust the regimen.
3. Add a long- or short-acting agent.

4. Rotate to another opioid.
5. Discontinue opioid therapy.

Of course, other therapeutics can be implemented as a result of the visit, such as instituting nonopioid analgesic approaches (e.g., acupuncture, physical therapy, psychological therapies, nonopioid analgesics).

Although this chapter is focused on prescribing practices that minimize the risks of opioid therapy, this can be effectively presented in the context of an overall approach to opioid therapy (see figure below). Opportunities to optimize outcome, by maximizing efficacy and minimizing risks, present themselves at every point of the algorithm and are be discussed in more detail below.

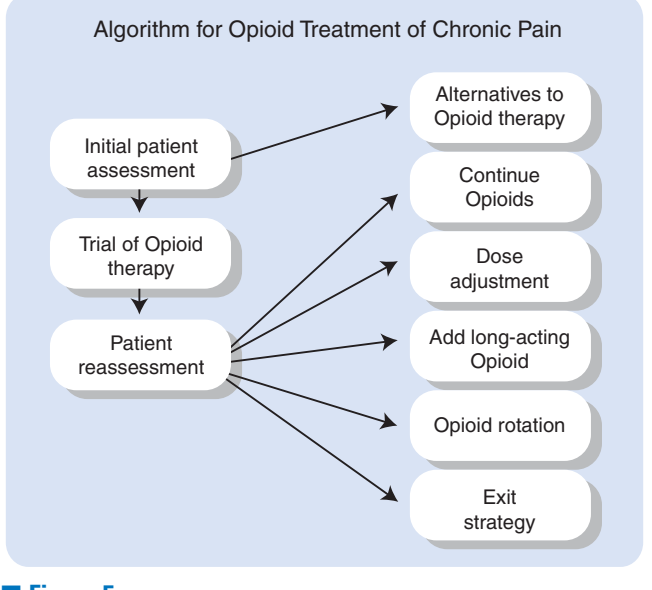

Figure 5.

Initial Patient Assessment

As in all other areas of medicine, the initial assessment of the patient with chronic pain has several purposes, including developing a diagnosis, cataloging previous therapies, understanding the patient's status on multiple dimensions (pain, function, psychological, social), setting treatment goals, and creating a treatment plan. With respect to opioid therapy, the purposes of the initial assessment are to determine whether opioid therapy is indicated, assess previous experience with opioid therapy, and determine the risk of opioid abuse. The table below indicates the key elements relevant to opioid therapy that should be added to the routine initial medical evaluation. With these additional elements of the medical history, the clinician can categorize patients into the following risk strata:

Low risk: no history of substance abuse; minimal if any risk factors
Can be managed by primary care provider

Medium risk: past history of substance abuse (no prescription opioid abuse); significant risk factors
Comanage with addiction and/or pain specialists

High risk: active substance abuse problem; history of prescription opioid abuse
Opioids may not be appropriate
Refer to center specializing in management of patients with comorbid pain and addictive disorders

Table 25.
Initial Evaluation Guide

History of present illness (pain)	Pain diagnosis
	Previous pain treatments
	Previous experience with opioid therapy
	Effectiveness on pain and function
	Compliance

(continued)

Table 25.
Initial Evaluation Guide (Continued)

History of present illness (pain) *(continued)*	Subjective experience with opioid therapy (e.g., euphoria)
	Use of opioids for nonprescribed purposes (insomnia, "stress," mood)
Past history	Illnesses relevant to opioid therapy (e.g., respiratory, hepatic, renal disease)
	Medical illnesses suggestive of substance abuse
	Hepatitis
	Human immunodeficiency virus infection
	Tuberculosis
	Cellulitis
	Sexually transmitted diseases
	Elevated liver function tests
	Trauma, burns
Psychiatric history	Current or past mental illness
	History of substance abuse, including alcohol, tobacco
	None
	Past, in remission
	Current
	Which substance(s), routes, prescription drugs
Social history	Arrests
	Motor vehicle accidents, driving under the influence
	Domestic violence
	Fires
	Contact with substance abusers
Family history	Substance abuse
	Family support

Initiating an Opioid Trial

If a patient appears to be an appropriate candidate for opioid therapy, it is appropriate to initiate a trial. In reality, many patients are prescribed opioids without a formal declaration of long-term opioid therapy. This occurs, for example, in a patient with chronic pain who receives a short-term opioid prescription for a pain flare and continues to receive frequent refills before the clinician (and patient) realize that, in fact, the patient is now on long-term opioid therapy. Although in principle these documented steps will be initiated at the time of initiation of opioid therapy, in practice, they are often initiated "when the light bulb goes off."

A written treatment agreement and the expressed informed consent of the patient are highly recommended when managing chronic pain with long-term opioid therapy. The physician should discuss the risks and benefits of the use of controlled substances with the patient, with persons designated by the patient, or with the patient's surrogate or guardian if the patient is incompetent.

The written treatment plan should state objectives and goals as well as expectations regarding behavior, limits, consequences, and stipulations, which may include (1) urine/serum medication levels screening when requested, (2) number and frequency of all prescription refills, and (3) reasons for which drug therapy may be discontinued (e.g., violation of agreement or lack of benefit). The contract should generally stipulate that the patient should receive prescriptions from one physician and one pharmacy. Treatment requires ongoing assessment and modifications of the treatment plan and agreed-on contract as appropriate.

Patients should be advised that opioid therapy is always considered a trial, and the advisability of continued opioid therapy, based on a risk–benefit assessment, is continually revisited for the duration of treatment, no matter how long. The spirit of these discussions is based on fundamental principles of medicine and entered into as a collaboration with the patient to maximize pain relief, functional outcomes, and goal attainment. These goals may be enhanced by opioid therapy

or may be undermined by opioid therapy—determining this is the purpose of the opioid trial. If opioids are found not to be helpful to the patient or the patient is unable to comply with therapy, the opioids will be discontinued in an appropriate manner because this is in the best interest of the patient.

An important difference between opioid therapy and nonabusable drug therapies is in the role of patient self-report. As is well known in the addiction community, the patient's self-report in the context of opioid therapy must be taken with a grain of salt because in a number of conditions, patient self-report loses its reliability; this applies to pain intensity, functional improvement, compliance with therapy, and substance abuse–related issues. The physician accustomed to obeying the mantra of "always believe the patient" must learn to modify this approach in the setting of opioid therapy and to consider self-report as one of many sources of information about the patient's status. Again, this is done for the sake of the patient.

A trial of opioid therapy is usually begun with as-needed doses of a short-acting product combining an opioid and a nonopioid analgesic. Common choices include hydrocodone/acetaminophen, oxycodone/acetaminophen, oxycodone/ibuprofen, and codeine/acetaminophen. The nonopioid component maximizes the balance of analgesia and side effects of the regimen. The use of short-acting as-needed doses allows the clinician and patient to assess the opioid requirement.

Short-acting agents are the most widely abused opioids in the United States. Long-acting products, with the exception of extended-release oxycodone products (e.g., OxyContin, due to the ease with which the extended-release formulation can be converted to a high-potency immediate-release formulation), tend to be less abused than short-acting preparations. Also, individuals with addictive disorders tend to be able to comply better with medications that are taken at fixed doses round the clock rather than on an as-needed basis. Therefore, in a patient at risk for substance abuse, an opioid trial at times may be more appropriately initiated with a transdermal opioid (e.g., fentanyl) or an extended-release oral formulation, although these products can certainly be abused as well. The patient's pain profile

should be taken into account as well: Patients with a fairly consistent pain profile (pain intensity is more or less the same all the time) are more likely to succeed with a sustained-release-only regimen; patients with intermittent pain may not do well.

A final consideration in the choice of opioid is tramadol. Tramadol is an analgesic that derives part of its pain-relieving properties from an opioid effect (just like morphine), but part from nonopioid effects (inhibition of reuptake of norepinephrine and serotonin, like many antidepressants). Tramadol is far less likely to be abused than other opioid analgesics, although it certainly can be abused. Tramadol is now available in an extended-release formulation as well. Patients with insufficient analgesia on tramadol can always be advanced to other opioid therapies.

No discussion of minimizing the risk of opioid therapies would be complete without discussing the nonabuse risks of opioids, such as constipation, nausea, vomiting, and dizziness. These side effects are very common early in opioid therapy and frequently cause patients to stop taking the prescription. Most guidelines call for implementing a prophylactic bowel regimen in all patients started on opioid therapy, although in patients at low risk for constipation, this can be held in reserve. Patients should be instructed to anticipate these side effects and given instructions on how to deal with them should they occur, potentially including a prescription for an antiemetic.

Follow-Up Visit

It is helpful to follow a structured assessment in following patients on long-term opioid therapy. Follow-up assessment that clinicians can use should be based on the "four A's":

1. Analgesia: What is the patient's average pain intensity?
2. Activities: How has the patient been functioning?
3. Adverse events: Has the patient had side effects?
4. Aberrant behavior: Has there been any evidence of abuse, misuse, or addiction?

Based on capturing the above information, the clinician can develop two more "A's": assessment and action plan.

Analgesia

Patients on opioids for chronic pain rarely enjoy complete pain relief. In fact, many patients live with pain in the "moderate" range—typically 4–7 on a 0–10 numerical rating scale—despite the common perception that opioids are extremely "strong" medications. It is critical to manage patient expectations early so that patients (and clinicians) are not disappointed with the result of partial pain relief and some functional restoration. *In the assessment of analgesia, at least partial pain reduction is necessary evidence for the appropriateness of continuing opioid therapy.* Many clinicians are familiar with the type of patient who, despite ongoing opioid therapy, continues to have reports of severe pain (8–10 out of 10), or even ratings that are "off the scale," but who insist that the opioids are "taking the edge off" the pain. These patients are at high risk for having psychosocial issues amplifying their pain perception and may constitute an exception to the generally useful dictum that in making decisions about analgesic regimens the clinician should rely primarily on the patient's self-report. Patients with persistently high pain intensity ratings and no evidence of functional improvement should have their dose increased (as long as there are not significant side effects), should have nonopioid analgesic approaches added (medical, rehabilitative, or psychosocial), or should be tapered off opioid therapy.

Activities

A judgment that a patient indeed is benefiting from opioid therapy is more convincing if there has been some evidence of functional improvement. Function can be construed broadly and includes activities of daily living, psychological function, social function, sleep, employment, and so forth. Even a slight improvement in pain intensity accompanied by clear evidence of increased function is very persuasive of opioid benefit. On the other hand, a picture of persistently high pain scores and no functional improvement—or actual functional deterioration—generally suggests that an opioid taper is appropriate.

Adverse Events

Patients have many more adverse effects of opioid therapy than they report. Therefore, adverse effects should be elicited prospectively. Often, patients fear that if they report side effects, the medication will be stopped. Although switching opioids is often the most effective solution for opioid-induced side effects, a number of other approaches can be used to address side effects without changing medications, and thereby improve the patient's outcome on opioid therapy.

One underappreciated side effect of long-term opioid therapy is endocrine disturbance. Most men and many women on long-term opioid therapy develop opioid-induced androgen deficiency (OPIAD), a form of central hypogonadism. In men, this is manifested by loss of libido, alteration in hair growth, mood disturbances, alteration of male role, loss of muscle strength and mass, and potentially osteoporosis and fractures. In women, the manifestations have been less well defined but may include alterations in menses and infertility. It is appropriate to measure the following on an annual basis for all patients on long-term opioid therapy: luteinizing hormone, follicle-stimulating hormone, total and free testosterone, sex hormone–binding globulin, and prolactin. It is also appropriate to screen for symptoms of OPIAD. There is no consensus on the management of OPIAD. A reasonable approach would be to switch opioids if feasible (although there is no information on whether one opioid is less likely to cause OPIAD than another); if OPIAD persists, and opioids remain indicated, then it is reasonable to supplement testosterone, preferably under the guidance of an endocrinologist.

Aberrant Behaviors

Many patients use their medication in a way that would not be condoned, or even anticipated by, their clinicians. Noncompliance is ubiquitous in medicine and may be unintentional (e.g., taking the wrong dose by mistake, forgetting a dose), intentional but not related to abuse (e.g., taking an extra Percocet to help sleep, unauthorized dose escalation for a pain flare), or intentional and related to abuse (taking

extra to get high, faking pain to get opioids, using the medication in an out-of-control manner). The clinician seeing the patient for pain often does not have the luxury that an addiction specialist in an addiction treatment center may have, whose patients all openly acknowledge their problematic drug use. The pain clinician often sees a confusing and subtle pattern of behaviors and needs to make a judgment as to whether the behaviors represent a pattern potentially indicating abuse, addiction, or criminal behavior, or whether the behaviors can be adequately explained by more benign causes: cognitive or language difficulties, administrative or insurance reasons, comorbid psychological conditions, or pseudoaddiction. Research has shown that most patients engage in a number of aberrant behaviors. The challenge is for the clinician to judge when these aberrant behaviors occur and what actions to take in view of the fact that confirmation can rarely be made with 100% certainty in the pain management setting.

Opioid Management Plan

Continuation of Opioid Therapy

Continuation of opioid therapy is not a default decision—it is a specific action that is justified by the patient assessment. Patients who have been stable with their dosing, who are benefiting in terms of pain reduction and/or improved function, who are tolerating their medication, and who have minimal aberrant behaviors are appropriate for continuation of therapy. Continuing therapy that is patently ineffective (whether or not it "takes the edge off") or that has been associated with functional deterioration (not explained by other factors) cannot be justified, whether or not there are other available management options.

Dose Adjustment

The dose can be too high, too low, or not administered optimally. Opioids need to be dosed on a case-by-case basis based on the response. Patients with persistent unrelieved pain, who are otherwise tolerating their doses, can have their dose increased. Patients

with dose-limiting side effects need to have their dose decreased, or their side effects managed another way; the dose cannot be increased. For some patients, the therapeutic index can be improved by altering the mode of administration. For example, patients with side effects at the peak of exposure to a short-acting opioid may do better with smaller, more frequent doses or with a long-acting opioid. In contrast, patients on long-acting opioids with side effects during periods of minimal pain may do better on intermittent doses of a short-acting opioid. Finally, some patients cannot find a dose that allows them to enjoy pain relief without significant side effects. Those patients are candidates for opioid rotation. If a therapeutic index cannot be found with a few opioids for an individual patient, that patient is probably not a candidate for opioid therapy and should be moved to "exit strategy."

Addition of a Long-Acting Opioid

There is little if any evidence that long-acting opioids are better in general than short-acting opioids for patients with chronic pain. However, there are particular types of patients for whom the addition of a long-acting opioid to a short-acting one, or even the substitution of long-acting for short-acting, may improve clinical outcomes. The clearest example is the patient who is taking substantial doses of short-acting opioids multiple times per day. Because tolerance is often first manifested by decreased duration of action, such patients may be forced to take their medication every 3 or even 2 hours. The addition of a long-acting agent may be extremely helpful. Another example is the patient with a compliance problem, due either to cognitive issues or abuse-related problems. Stopping the short-acting medication and substituting a long-acting medication may allow such patients to continue to benefit from opioid therapy in a manner that reduces risk. It is important for clinicians to realize that all currently marketed opioids can be abused, and substituting a long-acting opioid for a short-acting one may reduce risk in some circumstances but does not eliminate the risk completely. Further-

more, some long-acting opioids, such as extended-release oxycodone, are highly prized by abusers.

Opioid Rotation

It has been observed that individual patients may do poorly on one opioid but better after switching to another. Various explanations have been offered for this phenomenon. One holds that because some opioids are associated with the accumulation of toxic metabolites after prolonged use (e.g., morphine, hydromorphone), switching to another allows for the clearance of metabolites accumulated from the first opioid. Another theory is that different opioids may bind in different patterns to subtypes of the opioid receptor, providing different profiles of efficacy and side effects. Regardless, if a patient cannot seem to find an effective and well-tolerated dose of one opioid, it is reasonable to try one or two more opioids before giving up on opioid therapy or referring to a specialist for further management. It is of critical importance to note that switching patients who are on substantial doses of one opioid to another opioid can be tricky and, if done inappropriately, can lead to underdosing, severe painful flare-ups or withdrawal, or overdose and death, particularly with methadone. Clinicians should have a clear sense of their comfort zone with opioid rotation and should get input as needed.

Exit Strategy

When is it appropriate to stop opioid therapy in an individual patient? Although there has been little guidance on this issue, the following list of criteria is reasonable:

- There has been no convincing benefit from opioid therapy despite reasonable attempts at dose adjustment, management of side effects, and opioid rotation.
- Opioids cannot be tolerated at a dose that provides meaningful analgesia.
- Persistent compliance problems exist despite a patient treatment agreement and efforts at appropriate limit setting.

- Presence of a comorbid condition can make opioid therapy more likely to harm than help, such as an active substance abuse problem. (Note that the risk–benefit of opioid therapy depends as much on the treatment setting as on the patient and the medicine.)

It is critically important to distinguish between abandoning opioid therapy, abandoning pain management, and abandoning the patient. Exiting a patient from opioid therapy is often difficult for clinicians because of the patient's possible failure to understand that when this decision is made, it is for the welfare of the patient, not for the welfare of the doctor. Approaching the decision to taper off opioid therapy from the perspective of helping the patient in the long run helps avoid many (but not all) awkward confrontations. There are many other approaches to pain management than opioid therapy, and a patient can be tapered off from opioid therapy while alternative pain management approaches are pursued (albeit with reasonable expectations). Also, abandoning opioid therapy does not mean abandoning the patient. Often, the most reasonable course is to offer the patient continued medical guidance (without opioid therapy), even in the case of an addicted patient who pursues comanagement of the addictive disorder.

DOCUMENTATION

As in all cases, but especially when treating high-risk patients and those with substance-use disorders, the physician should keep accurate and complete records. Within the records, the following information should be included:

- The medical history and physical examination
- Diagnostic, therapeutic, and laboratory results
- Evaluations and consultations
- Treatment objectives
- Discussion of risks and benefits

- Treatments
- Medications (including date, type, dosage, and quantity prescribed)
- Instructions and agreements
- Periodic reviews

Records should remain current and be maintained in an accessible manner and readily available for review.

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This chapter is a summary of the following:

Katz NP, Inflexxion Inc. Patient Level Opioid Risk Management. 2007. http://www.PainEDU.org/manual.asp. Accessed July 30, 2007.

Glossary

Acute pain. The result of an injury or potential injury to body tissues and activation of nociceptive nerve fibers at the site of local tissue damage. This type of pain is usually time-limited and occurs after trauma, surgery, or a disease process. Acute pain is generally thought to have the biologic functions of alerting the individual to harm and preparing for the "fight-or-flight" response to danger.

Addiction. A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. Addiction involves a compulsive desire to use a drug despite continued harm.

Adjuvants. Pain-relieving medications whose primary indication traditionally is not for the treatment of pain. Adjuvants may be used to treat certain types of pain (e.g., neuropathic pain) or may be used to augment the analgesic effect of opioids or to manage their side effects. This term is derived mainly from the cancer pain literature and includes medications such as tricyclic antidepressants and anticonvulsants that were initially prescribed for other indications.

Allodynia. The presence of pain from a stimulus that is not normally painful. For example, pain caused by clothing or bedclothes rubbing over the skin would be considered allodynia.

Anergia. Lack of energy.

Anhedonia. Psychological condition characterized by the inability to derive pleasure from normally enjoyable activities. This is one indication of depression.

Anticonvulsants. Medications used to treat seizures. Due to presumed common mechanisms underlying epilepsy and neuropathic pain, many anticonvulsants are effective in treating neuropathic pain.

Antidepressants. A class of medications used to treat depression that includes tricyclic-type antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and monoamine

oxidase inhibitors. Some antidepressants, especially tricyclic-type antidepressants, have been found to have analgesic efficacy. Antidepressants are often used for treating depression associated with chronic pain conditions. See "Selective serotonin reuptake inhibitor" and "Tricyclic antidepressant" for more information. Other antidepressants in a miscellaneous category are bupropion, mirtazapine, nefazodone, and trazodone.

Antiemetic. Medication used for nausea and vomiting. Antiemetics are also used to facilitate treatment in migraine headaches that cause vomiting.

Biofeedback. Feedback from a device or computer to provide information about physiologic processes about which patients are not normally aware (e.g., muscle tension, skin temperature). Biofeedback may help relieve muscle tension caused by bracing muscles due to chronic pain.

Breakthrough pain. An exacerbation of pain that occurs beyond constant, background pain. Short-acting opioids are often prescribed for this purpose. One subcategory of breakthrough pain is "incident pain," which is pain by certain "incidents"—for example, walking.

Cancer pain. Pain associated with cancer that can be the result of cancer itself or treatments for cancer (surgery, radiation, chemotherapy). It can be visceral, somatic, or neuropathic in nature.

Catastrophizing. A cognitive coping style that involves an increasingly downward cycle of negative thoughts that has been associated with depression and negative outcomes in chronic pain.

Central sensitization. Process by which pain is amplified and maintained centrally (in the spinal cord or brain) in addition to the processes in peripheral tissues. This general concept is thought to underlie some types of allodynia or hyperalgesia. It may also explain why surgically removing the "cause of the pain" may not eliminate the pain.

Centralization. This is a loosely defined term of a pain process that begins in the periphery and over time becomes sustained partially or completely by central mechanisms. This concept overlaps with that of central sensitization. Centralization or central sensitization may also underlie evolution of the phenomenology of a chronic pain syndrome, such as the "spread" of reflex sympathetic dystrophy to other limbs.

Chronic pain. Pain that persists beyond the expected healing period. Chronic pain may be associated with levels of underlying pathology that do not explain the presence or extent of pain, and is often associated with affective and behavioral responses to the chronicity of the pain. Sources

often define chronic pain as that persisting beyond three or six months after an injury.

Cluster headaches. A strictly unilateral headache, usually occurring once or a few times a day at a characteristic time (e.g., 1 A.M.), lasting for 15–180 minutes, occurring in a series that lasts for weeks to months, separated by remissions lasting from months to years. Cluster headaches are usually episodic but have been known to last up to 14 days. Cluster headaches tend to occur more often in men, usually are one sided, but can shift from side to side in some patients.

Cognitions (thoughts). Cognitions can exert powerful effects on the patient's physical reactions, responses, and interpretations of pain.

Cognitive-behavioral therapy. A form of psychological treatment that combines cognitive psychotherapeutic techniques with behavioral techniques and is used to help patients change their thoughts and behaviors to increase coping with pain, decrease negative affect, and increase functioning.

Constipation. A condition in which bowel movements are infrequent or incomplete.

Complex regional pain syndrome type I (reflex sympathetic dystrophy). Chronic pain that includes clinical findings of regional pain, sensory changes, allodynia, abnormalities of temperature, abnormal pseudomotor activity, edema, and an abnormal skin color that occur after a noxious event.

Complex regional pain syndrome type II (causalgia). Includes all the features of complex regional pain syndrome type I as well as a peripheral nerve lesion.

Delirium. A syndrome characterized by combinations of cognitive deficits, fluctuating levels of consciousness, changes in sleep patterns, psychomotor agitation, hallucinations, delusions, and/or perceptual abnormalities. Causes are multifactorial and can include psychotropic medications, opioids, metabolic changes, cancer treatment, sepsis, or brain tumor or metastases.

Diabetic neuropathy. Damage or dysfunction of the peripheral nervous system due to diabetes mellitus. There are several distinct subtypes of diabetic neuropathy, each with different clinical features, prognosis, and treatment approaches. These include diabetic third cranial nerve palsy, diabetic radiculopathy, diabetic amyotrophy (radiculoplexopathy), and peripheral polyneuropathy (the classic "stocking-and-glove neuropathy"). Also see "Painful peripheral polyneuropathy."

Distraction. A cognitive coping technique that involves turning attention away from painful sensations.

Dyspareunia. Painful or difficult coitus.

Equianalgesic dose. The dose of one opioid that gives the same amount of pain relief as a dose of another opioid or another route of administration. For example, the equianalgesic dose of hydromorphone, for 10 mg of intramuscular morphine, is 1.5 mg intramuscularly. These comparisons are always averages and vary from patient to patient.

Full, or pure, agonists. Class of opioids that produce analgesic effects by binding to the mu opioid receptor. Opioid analgesics do not have a ceiling effect for analgesia and do not interfere with the effects of other opioids in this class when prescribed simultaneously. Examples include morphine, fentanyl, oxycodone, oxymorphone, hydromorphone, meperidine, codeine, and methadone. They are distinguished from the partial agonists, agonist/antagonists, and pure antagonists.

Heat. Refers to the application of heat via hot packs, hot water bottles, moist compresses, heating pads, chemical and gel packs, and immersion in water for the purpose of relief of pain.

Hyperalgesia. The phenomenon whereby stimuli that are normally painful produce exaggerated pain. It can be ascertained by the response to single and multiple pinpricks on neurologic examination.

Hyperpathia. A painful syndrome characterized by increased reaction to a stimulus, especially a repetitive stimulus, as well as increased threshold.

Hypopathia. Refers to decreased responses to stimulation.

Incident pain. Refers to the subset of breakthrough pain that is provoked by specific types of activity (e.g., walking, moving the arm).

Long-acting opioids. An opioid with a relatively long duration of action. By tradition, opioids that last longer than about 6–8 hours are referred to as *long-acting*, but the border between short- and long-acting is not precise. Long-acting opioids, also known as *slow-release* or *controlled-release opioids*, may have a long duration by virtue of their intrinsic pharmacokinetics (e.g., methadone), by having been formulated in a tablet that delivers the medication over a long period of time [e.g., morphine (Kadian), oxycodone (OxyContin)], or by having been formulated in another type of delivery system [e.g., fentanyl (Duragesic) patch]. Several opioids are available in both short- and long-acting forms (e.g., morphine, oxycodone, fentanyl).

Malingering. Intentional production of false or grossly exaggerated physical or psychological symptoms for the purpose of tangible external

incentives, such as obtaining financial compensation, evading criminal prosecution, avoiding work or military duty, and obtaining drugs.

Metabolite accumulation syndrome. Several opioids are metabolized to compounds that can accumulate and produce a characteristic syndrome. The features of this syndrome include anxiety, jitteriness, tremor, multifocal myoclonus, encephalopathy, convulsions, and death. This syndrome classically occurs with normeperidine, a metabolite of meperidine (Demerol), but has also been reported with morphine and hydromorphone. Other opioids have been reported to cause delirium and similar symptoms, but not due to metabolite accumulation, and without the other characteristic features noted above.

Mixed agonists/antagonists. Opioids that block opioid analgesia at the mu opioid receptor (mu) or are neutral at this receptor while simultaneously producing analgesia by activating the kappa receptor. Available agonist/antagonists include nalbuphine (Nubain), pentazocine (Talwin), and butorphanol (Stadol).

Modulation. The process of modification of nociceptive signals that takes place in the dorsal horn of the spinal cord and elsewhere with input from ascending and descending pathways.

Morphine conversion guide. A written guideline for the equianalgesic dosing of opioids.

Multimodal treatment. Treatment by more than one modality (e.g., physical therapy, medical, psychological).

Mucositis. Inflammation or sloughing of the oropharyngeal and gastrointestinal mucosae. This occurs stereotypically after bone marrow transplant and its related chemotherapy and is a well-recognized stereotypic severe pain syndrome.

Muscle de-education. Occurs when pain or avoiding pain leads to the failure to activate muscles or the abnormal activation of muscles in movement.

Myofascial pain. Pain localized to a region of muscle or soft tissue, associated with *trigger points* (palpable tender nodules or cords within the muscle). By definition, the pain must be reproduced by palpation of the trigger point, often with a referred component. The pain may be associated with subjective feelings of "numbness," "heaviness," and so forth, but no neurologic deficits. See also "Trigger points."

Neuropathic pain. Pain that is caused by a lesion or dysfunction of the nervous system.

Nociceptive pain. Pain that results from injury to or inflammation of somatic tissues.

Nonpharmacologic treatment. Treatment that does not involve use of drugs (e.g., physical therapy, biofeedback, psychological treatment).

Nonsteroidal antiinflammatory drug (NSAID). An aspirin-like drug used to reduce inflammation caused by injured tissue and pain.

Numerical Rating Scale (NRS). A method of rating pain intensity that involves written or verbal numerical notation of pain [e.g., 11-point scale from 0 ("no pain") to 10 ("pain as bad as it could be")].

Pain. An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Pain assessment. Evaluation of a variety of aspects of perceived sensations of pain, including intensity, duration, frequency, description, location, and emotional responses.

Pain behaviors. Verbal or nonverbal expressions including behavioral reactions such as grimacing, rubbing the affected part, guarding, or restricting movement and sighing.

Painful peripheral polyneuropathy. A generalized disorder of peripheral nerves, usually affecting the distal fibers, with proximal shading, typically occurring symmetrically. Peripheral polyneuropathies may be classified as axonal or demyelinating and have many causes, particularly metabolic and toxic. Certain types, such as diabetic, alcoholic, vasculitic, and idiopathic, tend to be most painful.

Palliative care. The supportive care of the terminal patient. Such support typically focuses on pain and symptom management, end-of-life psychological and social issues, coordinating care with the family, and preparing the family for grieving before and after the patient's death. Recently the term has been expanded to refer to management of pain and symptoms early in the course of illness before the patient is thought of as terminal.

Partial agonists. Opioid analgesics that produce analgesia by binding to the mu opioid receptor, but with less intrinsic efficacy at that receptor than "full agonists." These agents have a ceiling effect for analgesia and may precipitate withdrawal if administered to a physically dependent patient. Examples of partial agonists include nalbuphine, pentazocine, and butorphanol.

Pathophysiology. The physiology of abnormal states.

Peripheral sensitization. Process by which neurons in peripheral nerves become abnormally responsive to noxious or nonnoxious stimuli, thereby facilitating exaggerated pain perception.

Perception. The final process by which the subject integrates all nociceptive and modulating influences, in the context of psychological and social

background and situation information, to form the final experience of pain.

Pharmacological treatment of chronic pain. Treatment of pain with medicine.

Physical dependence. 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, or administration of an antagonist.

Physical therapy. Physical interventions, including passive modalities (e.g., application of heat and cold) and active modalities (e.g., range of motion, exercise) used to strengthen muscles, increase cardiovascular activity, and restore normal functioning.

Postherpetic neuralgia (PHN). Pain persisting beyond the healing of an acute herpes zoster rash. More recently, postherpetic neuralgia has been redefined by some as zoster-associated pain, recognizing that this is a spectrum of pain that occurs before, during, and for variable times after acute herpes zoster.

Primary afferent nociceptors. Pain receptors (A delta or C fibers) that respond to noxious mechanical, thermal, and chemical stimuli.

Primary headaches. Headaches that are autonomous without a specific lesion or disease process.

Pseudoaddiction. Is a term that is used to describe behavior that appears like addictive, "drug-seeking" behavior but is actually an effort to obtain pain relief. Behaviors from pseudoaddiction are said to be distinguished from addictive behaviors when the behaviors resolve after treatment of pain.

Psychiatric comorbidities. Concomitant psychiatric disorders that occur in individuals with a medical condition such as chronic pain.

Quantitative sensory testing (QST). Testing of sensations with calibrated stimuli such that both stimulus and response can be quantitated. In common usage, **quantitative sensory testing** refers to the use of devices that apply calibrated thermal (hot or cold) stimuli to the skin to record the patient's perception of thermal sensory and pain thresholds.

Referred pain. The perception of pain in parts of the body distant from the pathology from which the pain originates. Examples include arm pain during an acute myocardial infarction or eye pain during vertebral artery dissection.

Rest pain. Pain experienced while in an inactive or resting state.

Secondary headaches. Headache associated with primary disease processes, such as brain tumors, head trauma, vascular disorders, and substance use and withdrawal.

Silent nociceptors. Afferent nerves that do not respond to external stimulation unless inflammatory mediators are present.

Serotonin-adrenalin reuptake inhibitor (SNRI). A type of antidepressant that acts on different mechanisms than other types of antidepressants. An example is venlafaxine. Serotonin-norepinephrine reuptake inhibitor–type drugs are generally used to treat depression associated with chronic pain.

Somatoform disorder. Pain that is produced or amplified by psychological processes. Criteria are less restrictive than somatization disorder and require one or more physical complaints that cannot be explained by a general medical condition and cause significant social or occupational distress.

Somatic pain. Pain arising from somatic structures (e.g., skin, bones, muscle, joint). It is typically well-localized ("my left finger") and worsened by palpation or movement of the affected part.

Somatization disorder. Psychological disorder characterized by a pattern of multiple physical complaints (e.g., pain symptoms, gastrointestinal symptoms, sexual problems) present before the age of 30 that causes significant social and occupational impairment.

Selective serotonin reuptake inhibitor (SSRI). A type of antidepressant that is generally used to treat depression. Little evidence exists for the analgesic effects of selective serotonin reuptake inhibitors. Examples of medications in this class are citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

Stress management. Techniques designed to aid in the reduction of physiologic hyperarousal due to stress.

Transcutaneous electrical nerve stimulation (TENS). A pain reduction technique that involves applying low-voltage electrical stimulation to the skin, putatively stimulating large nerve fibers.

Tolerance. The loss of effect of a pharmacologic agent over a prolonged period of use, or the need to escalate the dose of the agent to maintain the same pharmacologic effect.

Topical analgesics. Analgesics that are applied to the skin or mucosa and act locally, presumably with insignificant systemic exposure. Examples include EMLA cream and the lidocaine patch.

Transdermal analgesics. Analgesics that are applied to the skin or mucosa, are systemically absorbed, and produce their therapeutic effects and side effects by systemic actions. Examples include the fentanyl patch and the buprenorphine patch.

Transduction. Process by which noxious stimulation of tissues is translated into neural signals in nociceptive nerve fibers. The deepest understanding of this process relates to the role of endogenous chemicals at afferent nerve endings in translating these stimuli (e.g., a burn) into nociceptive impulses.

Transmission. The process by which nerve signals from the periphery are sent to the dorsal horn of the spinal cord along the nociceptive afferents.

Tricyclic antidepressants. A class of antidepressant that is used clinically for treatment of neuropathic pain and for sleep disturbance, generally in lower doses than required for treating depression. Examples are amitriptyline, doxepin, imipramine, nortriptyline.

Trigger points. Tender nodules or cords within a muscle, palpation of which reproduces localized and/or radiating pain. Trigger points define *myofascial pain*. This phenomenon is distinct from *tender points*, which are tender areas of muscle or soft tissue *not associated* with palpable abnormalities in the texture of the muscle. Tender points occur in fibromyalgia and rheumatic diseases. See also "Myofascial pain."

Visceral pain. Refers to pain arising from pathology of the visceral organs, such as bowel obstruction or pancreatitis. Such pain is typically poorly localized (e.g., "My whole belly hurts") and is associated with visceral symptoms (e.g., nausea, vomiting).

Visual analogue scale (VAS). A method of measuring pain intensity that consists of a 10-cm line with anchors at the ends. Common anchors are "no pain" and "pain as bad as it could be." Patients draw a vertical line through the horizontal line and the result in centimeters is multiplied by 10, yielding a number between 0 and 100.

Windup. A process that has been observed in experimental animals whereby repeated stimulation of a peripheral structure (e.g., the skin) with an electric or other stimulus produces a greater and greater central response (e.g., pain). The mechanism of windup is thought to be sensitization of neurons in the spinal cord that receive nociceptive input, with the result that subsequent stimuli produce greater effects. Windup is an example of central sensitization, which is, in turn, an example of neural plasticity.

World Health Organization (WHO) analgesic ladder. Recommendations from the World Health Organization for titration of therapy for cancer pain, referred to as the "analgesic ladder." The ladder presents a three-step algorithm for using medications initially in the treatment of cancer pain and includes five major treatment concepts: (1) by the mouth, (2) by the clock, (3) by the ladder, (4) for the individual, and (5) with attention to detail.

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Appendix A
Dosing of Commonly Used Opioid Analgesics and Opioid Antagonists

	Recommended Starting Dose (Adults >50 kg)		Recommended Starting Dose (Child/Adult <50 kg)		Duration (in Hours)
	Oral	Parenteral	Oral	Parenteral	
Opioids					
Buprenorphine (IM: Buprenex, PO: Suboxone, Subutex)	2–8 mg sublingual	0.3 mg IM	Not recommended	0.004 mg/kg IM	6–8
Codeine phosphate/sulfate (codeine, in Tylenol with codeine, Phenaphen with codeine)	60 mg	60 mg IM/SC	1 mg/kg	Not recommended	4–6
Fentanyl citrate (IM: Sublimaze, TD: Duragesic, Ionsys, PO (transmucosal): Actiq, Fentora)	100–200 mcg trans-mucosal	50 mcg/hr TD 50–100 mcg IM	—	2–3 mcg/kg IM	1–2
Hydrocodone HCl (Lortab, Lorcet, CoGesic, Vicodin, others)	2.5–10 mg	—	0.2 mg/kg	—	4–8
Hydromorphone HCl (Dilaudid)	2–4 mg	1–2 mg SC 1–2 mg IM	0.06 mg/kg	0.015 mg/kg IM	4–5
Levorphanol tartrate (Levo-Dromoran)	2 mg	2 mg SC	0.04 mg/kg	0.02 mg/kg SC	6–8
Meperidine HCl (Demerol)	50–150 mg	100 mg SC 100 mg IM	1.1–1.8 mg/kg	0.75 mg/kg SC/IM	2–4
Methadone HCl (Dolophine, others)	20 mg	10 mg SC 10 mg IM	0.2 mg/kg	0.1 mg/kg SC/IM	4–6
Morphine sulfate (Morphine, MS Contin, Duramorph, Astramorph)	30 mg	10 mg SC 10 mg IM 2–4 mg IV	0.3 mg/kg	0.1 mg/kg SC/IM	3–6
Oxycodone HCl (Oxycontin, Roxicodone, in Percocet, Percodan, Roxicet, Tylox)	10 mg	—	0.2 mg/kg	—	4–6
Oxymorphone HCl (PR, SC, IM, IV: Numorphan)	Not available	1–1.5 mg SC 1–1.5 mg IM 0.5 mg IV 5 mg PR	Not recommended	Not recommended	3–6
PO: Opana	10 mg	—	Not recommended	—	3–6
PO: Opana-ER	5–10 mg	—	Not recommended	—	3–6
Propoxyphene Hcl (Darvon, in Genagesic, Wygesic)	65–100 mg	—	Not recommended	—	4–6
Tramadol HCl* (Ultram ER)	100 mg	—	Not recommended	—	24
Opioid antagonists					
Nalmefene (Revex)	—	*(for opioid overdose)* 0.5 mg/70 kg IV May give 1 mg/70 kg 2–5 mins later Max: 1.5 mg/70 kg	—	—	
Naloxone (Narcan, Nalone, Narcanti)	—	*(for opioid overdose)* 0.4–2 mg SC/IV q2–3min	—	*(for opioid overdose)* 0–5 yrs <20 kg: 0.1 mg/kg IV/IM, SC, ET q2–3min >5 yrs >20 kg: 2 mg IV, IM, SC, ET q2–3min	
Naltrexone (ReVia,Vivitrol)	*(for opioid addiction)* 50 mg qd	—	—	—	

HCl = hydrochloride; IM = intramuscular; ET = endotracheal; IV = intravenous; mcg = micrograms; PO = oral; PR = per rectum; SC = subcutaneous; TD = transdermal.
*A nonopioid, centrally acting analgesic.
Note: These tables propose suggested doses that are similar to morphine. Clinical response is the criterion that should be applied for each patient. Because there is not complete cross-tolerance among these drugs, it may be necessary to use a lower dose when changing drugs to re-titrate to response.
Caution: Opioid doses listed should not be used as initial starting doses in patients younger than 6 months of age. Review specific prescribing information recommended for these medications.

Appendix B
Dosing of Commonly Used Nonopioid Analgesics

Name	Dose	Comments
Acetaminophen (Tylenol)	PO/rectal 325–650 mg (6–12 mg/kg) q4 hr	Half-life (PO) 3–7 hr This is a readily available analgesic that typically does not produce gastric irritation or inhibit platelet function
Aspirin (Aspirin)	PO 325–650 mg (6–12 mg/kg) q4–8hr	Half-life (PO) 3–7 hr Causes irreversible platelet aggregation (for life of platelet: 7–10 days) resulting in prolonged bleeding time
Diclofenac (Voltaren)	PO 100–200 mg/day divided into 2 or 4 doses	Max: 200 mg/day Half-life: 1.9 hr
Celecoxib (Celebrex)*	PO 100–200 mg once or twice daily	Max: 400 mg/day Half-life: 11 hr A COX-2 inhibitor *Please review recent changes in recommended use of COX-2 inhibitors prior to prescribing
Diflunisal (Dolobid)	PO 1 gram then 500 mg q8–12hr	Max: 1500 mg/day Half-life: 8–12 hr
Etodolac (Generic)	PO 200–400 mg q6–8 hr	Max: 1,000 mg/day Half-life: 6.4 hr
Fenoprofen (Nalfon)	PO 200 mg (4 mg/kg) q4–6 hr	Max: 3200 mg/day Half-life: 3 hr
Ibuprofen (Advil)	PO 200–800 mg (8–16 mg/kg) q6 hr	Max: 2400 mg/day Half-life: 2 hr
Indomethacin (Indocin)	PO 25–50 mg (0.5–1 mg/kg) q6–12 hr	Max: 200 mg/day Half-life: 4.5 hr
Ketoprofen (Orudis)	PO 25–50 mg (0.5–1 mg/kg) q6–8 hr	Max: 75 mg/day Half-life: 2.1 hr
Ketorolac (Toradol)	Loading: IM/IV 30–60 mg (0.5–1 mg/kg) Maintenance: IM/IV 15–30 mg (0.25–0.5 mg/kg) PO 10 mg q4–6 hr	Max: 40 mg/day Half-life: 5.3 hr Minimize serious adverse side effects by limiting duration of use to 5 days
Meloxicam (Mobic)	PO 7.5–15 mg q24 hr	Max: 15 mg/day Half-life: 15–20 hr
Nabumetone (Relafen)	PO 1000–2000 mg per day (20–40 mg/kg/day) once daily or in two divided doses	Max; 2000 mg/day Half-life 24 hr
Naproxen (Naprosyn)	PO 500 mg (10 mg/kg), then 250 mg (5 mg/kg) q6–12 hr	Max: 1500 mg/day Half-life: 12–17 hr
Sulindac (Clinoril)	PO 100–200 mg bid	Max: 400 mg/day Half-life: 7.8 hr

Adapted from: Omoigui, S. *The Anesthesia Drugs Handbook.* St. Louis: Mosby. 1999.

Appendix C
Adjuvant Analgesic Agents

Drug	Usual Starting Dose and Interval	Common Dosage Range
Tricyclic antidepressants		
Amitriptyline (Elavil)	25 mg PO hs (10 mg in frail, elderly)	50–150 PO hs
Desipramine (Norpramin, Pertofrane)	25 mg PO hs (10 mg in frail, elderly)	50–200 PO hs
Nortriptyline (Aventyl, Pamelor)	25 mg PO hs (10 mg in frail, elderly)	50–150 PO hs
Anticonvulsants		
Carbamazepine (Tegretol)	100 mg PO bid	200 mg PO bid–qid
Clonazepam (Klonopin)	0.25–0.5 PO tid	0.5–1 mg PO tid
Duloxetine (Cymbalta) (for diabetic peripheral neuropathy)	PO 40–60 mg/day; may increase to 120 mg PO if tolerated but no response	120 mg/day
Gabapentin (Neurontin)	100 mg PO tid; increase by 100 mg tid every 3 days	300–3,600 mg/day in three divided doses
Phenytoin (Dilantin)	300 mg PO qd or 100 mg PO tid	300–400 mg/day
Pregabalin (Lyrica) (for neuropathic pain, diabetic peripheral neuropathy)	PO 100 mg tid; start 50 mg tid; increase to 300 mg/day over 7 days	Max: 300 mg/day
Valproic acid (Depakene)	125 mg PO tid	500–1,000 mg PO tid
Divalproex (Depakote)		
Anxiolytics—benzodiazepines (Note: All benzodiazepines cause addictive sedation with opioids.)		
Alprazolam (Xanax)	0.25–0.5 mg PO qd–tid	Minimum effective dose
Chlordiazepoxide (Librium)	10–25 mg PO qd–tid	Minimum effective dose
Diazepam (Valium)	5–10 mg PO qd–bid	Minimum effective dose
Lorazepam (Ativan)	0.5–2 mg PO qd–tid	Minimum effective dose
Midazolam (Versed)	Doses vary depending on individual patient needs	
Anxiolytics—azapirones		
Buspirone (BuSpar)	5 mg PO tid	Max: 60 mg/day
Psychostimulants		
Dextroamphetamine (Dexedrine)	2.5–5 mg PO qd or bid; last dose before 2 P.M.	5–20 in divided doses; last dose before 2 PM
Methylphenidate (Ritalin)	2.5–5 mg PO qd or bid; last dose before 2 P.M.	5–20 in divided doses; last dose before 2 PM
Corticosteroids		
Dexamethasone	Dexamethasone, 40–100 mg IV or equivalent as loading doses or q6h for first 24–72 hrs (if indications are acute spinal cord injury)	Dexamethasone, 10–20 mg IV q6h or methylprednisolone, 40–80 mg IV q6h
Methylprednisolone	Dexamethasone, 4–8 mg PO q8–12h Prednisone, 20–40 mg PO q8–12h (if indications are nerve compression, visceral distension, increased ICP, soft tissue infiltration) Dexamethasone, 4–12 mg/day Prednisone, 5–10 mg tid (if indications are alleviation of nausea, anorexia, pain in palliative care)	Minimal effective dose
Miscellaneous adjuvant analgesic agents		
Baclofen (Lioresal, Atrofen)	5–10 mg PO tid–qid intrathecal infusions	Maximum oral dose = 80–120 mg/day Intrathecal: 300–800 mcg/day
Clonidine (Duraclon)	30 mcg/hr (epidural)	Doses >40 mcg/hr not well studied
Mexiletine (Mexitil)	150–300 mg PO tid	150–300 mg PO tid
Octreotide (Sandostatin)	50–100 mcg SC bid–tid	Varies
Pamidronate (Aredia)	90 mg IV every 4 weeks	90 mg IV every 4 weeks proved effective

bid = twice each day; hs = at bedtime; ICP = intracranial pressure; IV = intravenously; PO = by mouth; qd = once each day; qid = four times a day; SC = subcutaneously; tid = three times a day.
Adapted from Scott CJ, Griffin CB. *Pain Management Tables and Guidelines.* Boston: Dana-Farber Cancer Institute/Brigham & Women's Hospital. 2000.

Appendices
(fold out)