Pain:

Current Understanding of Assessment, Management, and Treatments

NATIONAL
PHARMACEUTICAL
COUNCIL, INC

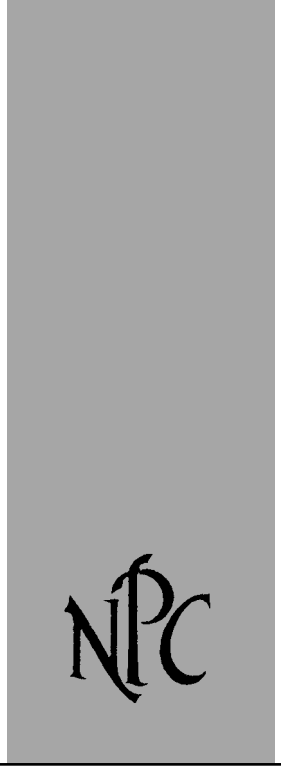
Joint Commission
on Accreditation of Healthcare Organizations

This monograph was developed by NPC as part of a collaborative project with JCAHO.

December 2001

DISCLAIMER: This monograph was developed by the National Pharmaceutical Council (NPC) for which it is solely responsible. Another monograph related to measuring and improving performance in pain management was developed by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) for which it is solely responsible. The two monographs were produced under a collaborative project between NPC and JCAHO and are jointly distributed. The goal of the collaborative project is to improve the quality of pain management in health care organizations.

This monograph is designed for informational purposes only and is not intended as a substitute for medical or professional advice. Readers are urged to consult a qualified health care professional before making decisions on any specific matter, particularly if it involves clinical practice. The inclusion of any reference in this monograph should not be construed as an endorsement of any of the treatments, programs or other information discussed therein. NPC has worked to ensure that this monograph contains useful information, but this monograph is not intended as a comprehensive source of all relevant information. In addition, because the information contain herein is derived from many sources, NPC cannot guarantee that the information is completely accurate or error free. NPC is not responsible for any claims or losses arising from the use of, or from any errors or omissions in, this monograph.



Section I:

Background and Significance

A. Introduction

After years of neglect, issues of pain assessment and management have captured the attention of both health care professionals and the public. Factors that prompted such attention include the high prevalence of pain, continuing evidence that pain is undertreated, and a growing awareness of the adverse consequences of inadequately managed pain.

Pain is common. About 9 in 10 Americans regularly suffer from pain,[1] and pain is the most common reason individuals seek health care.[2] Each year, an estimated 25 million Americans experience acute pain due to injury or surgery and another 50 million suffer chronic pain.[3,4] Chronic pain is the most common cause of long-term disability, and almost one third of all Americans will experience severe chronic pain at some point in their lives.[5] As the population ages, the number of people who will need treatment for pain from back disorders, degenerative joint diseases, rheumatologic conditions, visceral diseases, and cancer is expected to rise.[5]

Pain is often undertreated. Improved understanding of pain mechanisms has advanced treatment for pain. Sufficient knowledge and resources exist to manage pain in an estimated 90% of individuals with acute or cancer pain.[6] Safe and effective medical treatment for many types of chronic pain also is available.[7] Yet recent studies, reports, and a position statement[2,8-9] suggest that many types of pain (e.g., postoperative pain, cancer pain, chronic noncancer pain) and patient populations (e.g., elderly patients, children, minorities, substance abusers)[10-11] are undertreated. Data from a 1999 survey suggest that only 1 in 4 individuals with pain receive appropriate therapy.[4,12]

Inadequate pain management has adverse consequences. The adverse consequences of undertreated pain are considerable. Poorly managed acute pain may cause serious medical complications (e.g., pneumonia, deep venous thrombosis), impair recovery from injury or procedures, and/or progress to chronic pain.[13] Undertreated chronic pain can impair an individual's ability to carry out daily activities and diminish quality of life.[14] In addition to disability, undertreated pain causes significant suffering. Individuals with poorly controlled pain may experience anxiety, fear, anger, or depression.[15] Pain is also a major cause of work absenteeism, underemployment, and unemployment.[2] Mounting health care costs and disability compensation reflect, in part, poor care for pain-related conditions.[16] Thus, undertreated pain has significant physical, psychological, and financial consequences.

The undertreatment of pain is not a new problem. The Agency for Health Care Policy and Research (AHCPR)[a] published the first clinical practice guideline (CPG) for pain management in 1992. The authors of this guideline acknowledged the prior efforts of multiple health care disciplines (e.g., surgery, anesthesiology, nursing) and pain management groups (e.g., American Pain Society, International Association for the Study of Pain) to address this situation.[13] Multiple groups have subsequently produced CPGs that address the management of many types of pain. The recently introduced Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards for pain assessment and management[17] represent a giant step forward in improving pain management.[b]

To facilitate these efforts, this monograph has two primary objectives: 1) to provide practical knowledge that will enhance the reader's understanding and management of pain and 2) to introduce some strategies to improve pain management (e.g., CPGs, standards), as further explored in monograph 2. Due to the breadth and complexity of the subject matter, a comprehensive discussion of all aspects of pain assessment and management is beyond the scope of this monograph. The scope and potential limitations of this monograph are as follows:

- The neurological and psychological mechanisms that underlie pain are complex, and knowledge of mechanisms is limited. The discussion of pathophysiology in this monograph emphasizes practical knowledge that will facilitate diagnosis and/or the selection of appropriate interventions.
- Controversy exists over how both pain and analgesics should be classified. This monograph reviews only a few of the many classification systems.
- Various factors (e.g., insufficient funding for studies, lack of good diagnostic codes) limit the availability of current, reliable epidemiological data related to pain.
- A host of factors, including the setting, characteristics of the pain, and patient factors (e.g., age, medical condition, language and cognitive abilities) influence pain

[a] The Agency for Health Care Policy and Research is now the Agency for Healthcare Research and Quality.

[b] These JCAHO standards first appeared in the 2000-2001 JCAHO standards manual and apply to ambulatory care, behavioral health, managed behavioral health, health care networks, home care, hospitals, long-term care organizations, and pharmacies.

assessment. This monograph provides an overview of pain assessment, but primarily focuses on the initial assessment.
- Many strategies exist to manage various types of pain. This monograph reviews pharmacologic and nonpharmacologic treatments for pain, with greater emphasis on the former. Specific information about the treatment of certain conditions is limited to some common and treatable types of pain. Coverage of treatment issues relevant to special populations (e.g., children, the elderly) is limited.
- The discussion of pharmacologic treatments emphasizes: 1) the major classes of drugs used for pain management; 2) examples and salient features of these drugs; and 3) some means of ensuring the safe, strategic, and effective use of these agents. However, this information is only an overview. The reader should consult CPGs for specific guidance in managing patients.
- Due to the large volume of associated literature, a review of the mechanisms, assessment, and management of pain associated with some conditions (e.g., cancer) is beyond the scope of this monograph. This monograph focuses on the pathophysiology, epidemiology, assessment, and treatment of acute pain and chronic noncancer pain (CNCP).

B. Definitions and Mechanisms of Pain

This section of the monograph explores mechanisms that underlie the perception of pain. It also reviews a pain classification system based on underlying pathophysiology. The goal is to provide practical information that will facilitate pain assessment and management. A question-and-answer format is used to provide information about the following:
- The definition of pain
- The process by which noxious stimuli generate neural signals and the transmission of these signals to higher centers (nociception)
- The role of inflammatory mediators, neurotransmitters, and neuropeptides in these processes (i.e., targets of many pharmacologic therapies)
- Definitions and causes of some clinical pain states
- Underlying mechanisms and characteristics of somatic pain, visceral pain, and neuropathic pain.

1. What Is Pain?

In 1968, McCaffery defined pain as "whatever the experiencing person says it is, existing whenever s/he says it does".[18] This definition emphasizes that pain is a subjective experience with no objective measures. It also stresses that the patient, not clinician, is the authority on the pain and that his or her self-report is the most reliable indicator of pain.[13] In 1979, the International Association for the Study of Pain (IASP) introduced the most widely used definition of pain. The IASP defined pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[19] This definition emphasizes that pain is a complex experience that includes multiple dimensions.

2. How Does Injury Lead to Pain?

Nociception refers to the process by which information about tissue damage is conveyed to the central nervous system (CNS). Exactly how this information is ultimately perceived as painful is unclear. In addition, there can be pain without nociception (e.g., phantom limb pain) and nociception without pain. But classic descriptions of pain typically include four processes:[20-23]
- *Transduction:* the conversion of the energy from a noxious thermal, mechanical, or chemical stimulus into electrical energy (nerve impulses) by sensory receptors called nociceptors
- *Transmission:* the transmission of these neural signals from the site of transduction (periphery) to the spinal cord and brain
- *Perception:* the appreciation of signals arriving in higher structures as pain
- *Modulation*: descending inhibitory and facilitory input from the brain that influences (modulates) nociceptive transmission at the level of the spinal cord.

3. What Happens During Transduction?

a. Nociceptor activation and sensitization

Nociceptors are sensory receptors that are preferentially sensitive to tissue trauma or a stimulus that would damage tissue if prolonged.[19] These receptors are the free endings of (primary afferent) nerve fibers distributed throughout the periphery (Figure 1). Signals from these nociceptors travel primarily along two fiber types: slowly conducting unmyelinated C-fibers and small, myelinated, and more rapidly conducting A-delta fibers[c] (Figure 2).

Injury to tissue causes cells to break down and release various tissue byproducts and mediators of inflammation (e.g., prostaglandins, substance P, bradykinin, histamine, serotonin, cytokines).[24,25] Some of these substances activate nociceptors (i.e., cause them to generate nerve impulses) and most sensitize nociceptors (i.e., increase their excitability and discharge frequency).[26,27] Ongoing activation of nociceptors may cause nociceptive pain (see I.B.9). Peripheral (nociceptor) sensitization amplifies signal transmission and thereby contributes to central sensitization and clinical pain states (see I.B.7-8).[28]

[c]In addition to these nociceptors, A-beta fibers (which normally subserve touch) sometimes act as nociceptors when sensitized. The functioning of nociceptors depends upon the electrophysiological properties of the tissues, co-factors, and cytokines.[24]

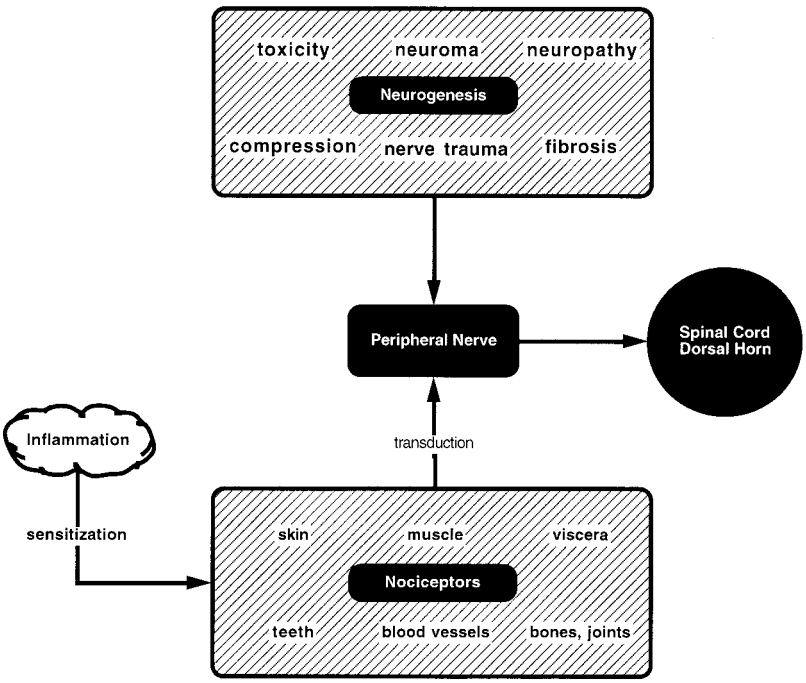
b. Peripheral neuropathic pain

Not all pain that originates in the periphery is nociceptive pain. Some neuropathic pain is caused by injury or dysfunction of the peripheral nervous system (i.e., peripheral nerves, ganglia, and nerve plexi)(see I.B.10)(Figure 1).[22]

c. Clinical implications

Some analgesics target the inflammatory process that produces sensitization. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX), thus decreasing the synthesis of prostaglandins.[29-30] Other analgesics (e.g., antiepileptic drugs, local anesthetics) block or modulate channels, thus inhibiting the generation of nerve impulses.

Figure 1.



Source: Reference 22.

Peripheral origins of pain. Noxious signaling may result from either abnormal firing patterns due to damage or disease in the peripheral nerves or stimulation of nociceptors (free nerve endings due to tissue trauma). Inflammation in injured or diseased tissue sensitizes nociceptors, lowering their firing thresholds. Some clinical pain states have no peripheral origin, arising from disorders of brain function.

4. What Is Transmission?

Nerve impulses generated in the periphery are transmitted to the spinal cord and brain in several phases:[21,31]

a. Periphery to the spinal cord

Most sensory nerve impulses travel via the nerve processes (axons) of primary afferent neurons to the dorsal horn (DH) of the spinal cord (Figure 2).[32] There, primary afferent neurons propagate nerve impulses to DH neurons through the release of excitatory amino acids (EAAs) (e.g., glutamate, aspartate) and neuropeptides (e.g., substance P) at synapses (connections) between cells.[d,39] Activated DH projection neurons forward nociceptive impulses toward the brain.

However, not all events in the DH facilitate nociception. Spinal interneurons release inhibitory amino acids (e.g., γ-aminobutyric acid [GABA]) and neuropeptides (endogenous opioids) that bind to receptors on primary afferent and DH neurons and inhibit nociceptive transmission by presynaptic and postsynaptic mechanisms.[39-42] Descending inhibitory input from the brain also modulates DH nociceptive transmission (see I.B.6) (**Figure 3**). Thus, nociceptive traffic in the DH is not merely relayed to higher centers but rather is heavily modulated. These inhibitory events are part of a natural nociceptive-modulating system that counterbalances the activity of the nociceptive-signaling system.

[d]The excitatory amino acids (EAAs) glutamate and aspartate mediate most excitatory transmission in the CNS, including that related to nociception.[33] The neuropeptide substance P activates spinal neurons and enhances their responsiveness to EAA, thus also facilitating nociception.[34-38]

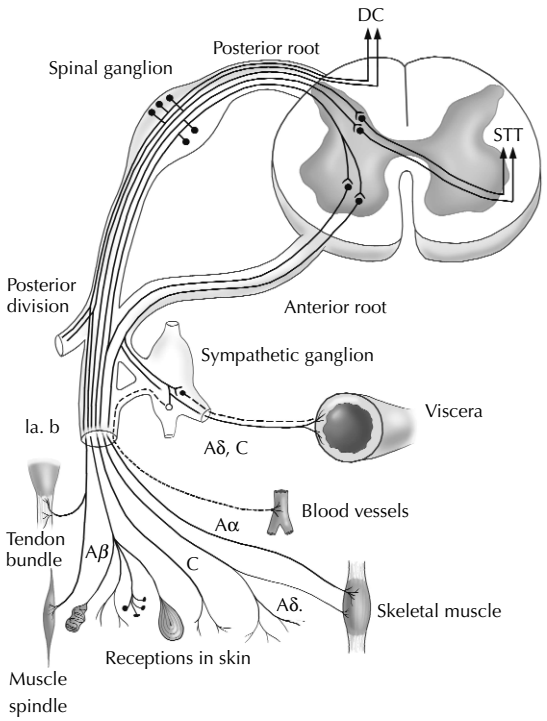
b. Spinal cord to the brain

The nerve processes of DH projection neurons project to the brain in bundles called ascending tracts. Projection neurons from some DH regions transmit nociceptive signals to the thalamus via the spinothalamic tract (STT) (Figures 2, 4).[39,43] Others transmit nociceptive information to the reticular formation, mesencephalon, and hypothalamus via the spinoreticular, spinomesencephalic, and spinohypothalamic tracts (Figure 4).[22,44]

c. Clinical implications

Some analgesics inhibit nociception in the

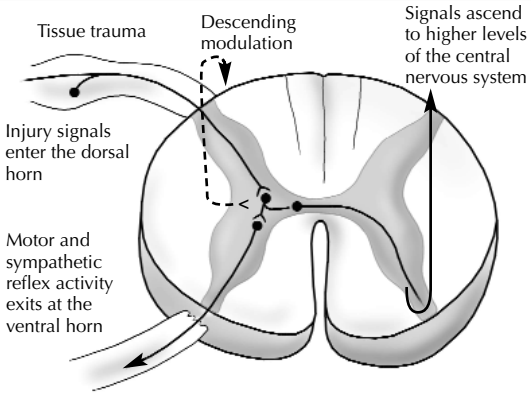
Figure 2.



Source: Reference 39.

A simplified schema of a spinal nerve and the different types of fibers contained therein. (DC: dorsal columns; STT: spinothlamic tract).

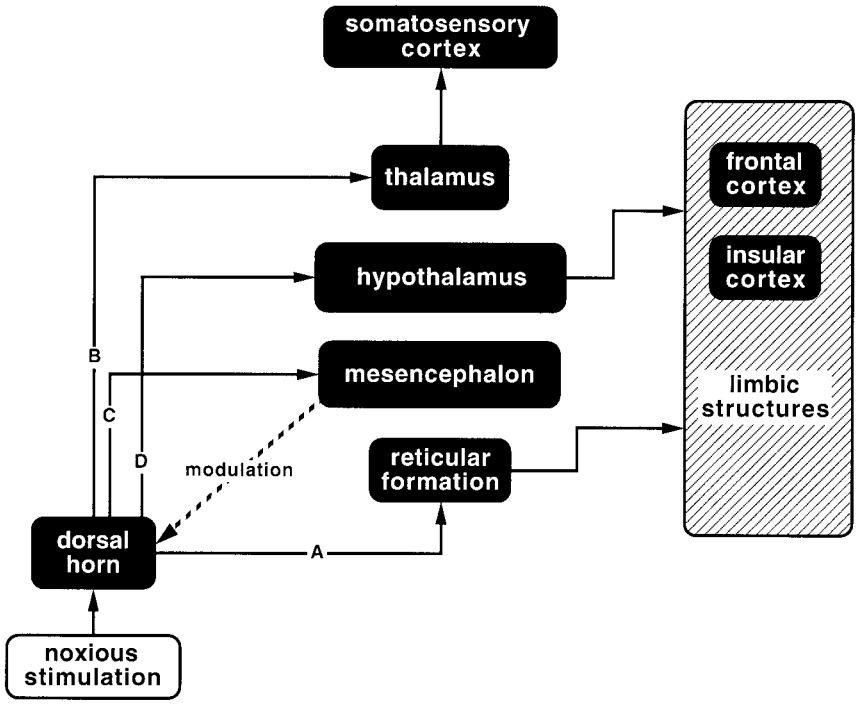
Figure 3.



Source: Reference 22.

A simplified view of spinal cord mechanisms. Afferents conveying noxious signaling from the periphery enter the dorsal horn of the spinal cord, where they synapse with dorsal horn neurons. This generates nerve impulses that exit the cord ipsilaterally through motor and sympathetic efferents. Other activity produces signals that ascend to various areas in the brain. This simple sketch shows only the anterolateral funiculus, which ascends to the brain stem and thalamus. Inhibitory influences include certain spinal interneurons and descending pathways from periadqueductal gray and other areas (dashed line).

Figure 4.



Source: Reference 22.

Multiple pathways of nociceptive transmission for the spinal cord to central structures. There are four major pathways the A: spinoreticular; B: spinothalamic; C: spinomesencephalic; and D: spinohypothalamic tracts.

DH. For example, opioid analgesics bind to opioid receptors on primary afferent and DH neurons and mimic the inhibitory effects of endogenous opioids. They also bind to opioid receptors in the brain and activate descending pathways that further inhibit DH nociceptive transmission.[45] Baclofen, a GABA agonist, binds to $GABA_B$ receptors and mimics the inhibitory effects of GABA on nociceptive transmission.[46]

5. What Is Perception?

The perception of pain is an uncomfortable awareness of some part of the body, characterized by a distinctly unpleasant sensation and negative emotion best described as threat. Both cortical and limbic system structures are involved.[47] Nociceptive information from some DH projection neurons travels via the thalamus to the contralateral somatosensory cortex[39] (Figure 4), where input is somatotopically mapped to preserve information about the location, intensity, and quality of the pain.[43,48] The thalamus relays other nociceptive input to the limbic system.[44] This input joins input from the spinoreticular and spinomesencephalic tracts to mediate affective aspects of pain.[20] Immediate social and environmental context influences the perception of pain, as do past experience and culture. Consequently, a standard cause of pain (e.g., surgery) can generate enormous individual differences in pain perception.

6. What Is Modulation?

a. Descending pathways

Modulation of nociceptive transmission occurs at multiple (peripheral, spinal, supraspinal) levels. Yet, historically, modulation has been viewed as the attenuation of DH transmission by descending inhibitory input from the brain. Melzack and Wall's Gate Control Theory brought this notion to the forefront in 1965.[49] Models of descending pain systems now include both inhibitory and facilitory descending pathways.

Multiple brain regions contribute to descending inhibitory pathways.[39] Nerve fibers from these pathways release inhibitory substances (e.g., endogenous opioids, serotonin, norepinephrine, GABA) at synapses with other neurons in the DH. These substances bind to receptors on primary afferent and/or DH neurons and inhibit nociceptive transmission. Such endogenous modulation may contribute to the wide variations in pain perception observed among patients with similar injuries.[20,50-51]

b. Clinical implications

Some analgesics enhance the effects of descending inhibitory input. For example, some antidepressants interfere with the reuptake of serotonin and norepinephrine at synapses, increasing their relative interstitial concentration (availability)[52-53] and the activity of endogenous pain-modulating pathways.[21,50,53a] Thus, some, but not all, antidepressants are used to treat some types of chronic pain.

7. What Is Peripheral Sensitization?

Inflammatory mediators, intense, repeated, or prolonged noxious stimulation, or both can sensitize nociceptors.[26,54-55] Sensitized nociceptors exhibit a lowered threshold for activation and an increased rate of firing.[25,56-57] In other words, they generate nerve impulses more readily and more often. Peripheral (nociceptor) sensitization plays an important role in central sensitization and clinical pain states such as hyperalgesia (increased response to a painful stimulus) and allodynia (pain caused by a normally innocuous stimulus).[58-59]

8. What Is Central Sensitization?

a. Definitions and features

Central sensitization refers to a state of spinal neuron hyperexcitability.[60] Tissue injury (inflammation), nerve injury (i.e., aberrant neural input), or both may cause it,[27] and ongoing nociceptive input from the periphery is needed to maintain it.[48] Repeated stimulation of C-nociceptors initially causes a gradual increase in the frequency of DH neuron firing known as "wind-up."[61] Activation of N-methyl D-aspartate (NMDA) receptors[e] plays a key role in this process.[27,64-65] The clinical correlate of wind-up-temporal summation-refers to a progressive increase in pain experienced over the course of a repeated stimulus.[66]

Repeated or prolonged input from C-nociceptors or damaged nerves causes a longer-lasting increase in DH neuron excitability and responsiveness (i.e., central sensitization[f])[67,75] which may outlast the stimulus by minutes to hours.[38] Central sensitization is associated with a reduction in central inhibition, spontaneous DH neuron activity, the recruitment of responses from neurons that normally only respond to low-intensity stimuli (i.e., altered neural connections), and expansion of DH neuron receptive fields.[27,60,67,76-78] Clinically, these changes may manifest as: 1) an increased response to a noxious stimulus (hyperalgesia), 2) a painful response to a normally innocuous stimulus (allodynia), 3) prolonged pain after a transient stimulus (persistent pain), and 4) the spread of pain to uninjured tissue (i.e., referred pain).[60,79] In contrast to hyperalgesia caused by peripheral mechanisms (i.e., primary hyperalgesia), such secondary hyperalgesia extends beyond the region of injury.[48,80]

b. Clinical implications

Sensitization is likely responsible for most of the continuing pain and hyperalgesia after an injury.[81] This sensitivity may be due to "normal" noxious input from injured and inflamed tissue or "abnormal" input from injured nerves or ganglia. In the former case, sensitization serves an adaptive purpose. That is, the hyperalgesia and allodynia encourage protection of the injury during the healing phase. However, these processes can persist long after healing of the injury in the setting of chronic pain.

Central sensitization plays a key role in some chronic pain, especially pain induced by nerve injury or dysfunction (i.e., neuropathic pain). It explains why neuropathic pain often exceeds the provoking stimulus, both spatially and temporally.[48,60] Central sensitization also explains the long-standing observation that established pain is more

[e]Early transient changes include removal of the voltage-dependent magnesium blockade of NMDA receptors. This permits glutamate to activate NMDA receptors, with subsequent temporal summation of slow synaptic potentials that manifests as wind-up.[27,62-63]

[f]Central sensitization reflects a complex series of changes that may begin with the release of excitatory substances (e.g., glutamate, substance P) from cells following noxious stimulation. These substances activate NMDA and non-NMDA (NK) receptors, which increases intracellular calcium levels[67-70] and activates calcium-dependent intracellular kinases.[38,71] These kinases break down arachidonic acid (releasing byproducts)[72] and phosphorylate ion channels and NMDA receptors. Potential consequences of these changes include altered synaptic transfer and gene expression (e.g., c-fos).[27,60,73-74] Collectively, these changes may promote long-lasting increases in DH neuron excitability (i.e., central sensitization).

difficult to suppress than acute pain.[13,75,82-83]

In contrast to nociceptive pain, neuropathic pain is often unresponsive or poorly responsive to NSAIDs and opioids.[84-85] However, it may respond to antiepileptic drugs, antidepressants, or local anesthetics.[86]

9. What Is Nociceptive Pain?

Pain that is classified on the basis of its presumed underlying pathophysiology is broadly categorized as nociceptive or neuropathic pain.[87] Nociceptive pain is caused by the ongoing activation of A-δ and C-nociceptors in response to a noxious stimulus (e.g., injury, disease, inflammation).[88] Pain arising from visceral organs is called visceral pain, whereas that arising from tissues such as skin, muscle, joint capsules, and bone is called somatic pain. Somatic pain may be further categorized as superficial (cutaneous) or deep somatic pain (Table 1).

In contrast to neuropathic pain, the nervous system associated with nociceptive pain is functioning properly. Generally, there is a close correspondence between pain perception and stimulus intensity, and the pain is indicative of real or potential tissue damage. Differences in how stimuli are processed across tissue types contribute to the pain's varying characteristics (Table 1).[22] For example, cutaneous pain is often described as a well-localized sharp, pricking, or burning sensation; deep somatic pain, as a diffuse dull or aching sensation; and visceral pain, as a deep cramping sensation that may be referred to other sites (i.e., referred pain).[88] Associated clinical pain states (e.g., hyperalgesia, allodynia) reflect sensitization (see I.B.7-8).[88,90]

10. What Is Neuropathic Pain?

Neuropathic pain is caused by aberrant signal processing in the peripheral or central nervous system.[g,96] In other words, neuropathic pain reflects nervous system injury or impairment. Common causes of neuropathic pain include trauma, inflammation, metabolic diseases (e.g., diabetes), infections (e.g., herpes zoster), tumors, toxins, and primary neurological diseases.[81] Neuropathic pain can be broadly categorized as peripheral or central

[8]Data from animal studies suggest that the following changes may contribute to neuropathic pain: 1) generation of spontaneous ectopic activity, 2) loss of normal inhibitory mechanisms in the dorsal horn (i.e., central disinhibition), 3) altered primary afferent neuron phenotypes, and 4) sprouting of nerve fibers (i.e., altered neural connections).[27,63-91-95] Collectively, these changes cause abnormal nerve impulse firing and/or abnormal signal amplification.[48]

Table 1. Examples and Characteristics of Nociceptive Pain

	Superficial Somatic Pain	Deep Somatic Pain	Visceral Pain
Nociceptor location	Skin, subcutaneous tissue, and mucous membranes	Muscles, tendons, joints, fasciae, and bones	Visceral organs[a]
Potential stimuli	External mechanical, chemical, or thermal events Dermatologic disorders	Overuse strain, mechanical injury, cramping, ischemia, inflammation	Organ distension, muscle spasm, traction, ischemia, inflammation
Localization	Well localized	Localized or diffuse and radiating	Well or poorly localized
Quality	Sharp, pricking, or burning sensation	Usually dull or aching, cramping	Deep aching or sharp stabbing pain, which is often referred to cutaneous sites
Associated symptoms and signs	Cutaneous tenderness, hyperalgesia hyperesthesia, allodynia	Tenderness, reflex muscle spasm, and sympathetic hyperactivity[b]	Malaise, nausea, vomiting, sweating, tenderness, reflex muscle spasm
Clinical examples	Sunburn, chemical or thermal burns, cuts and contusions of the skin	Arthritis pain, tendonitis, myofascial pain	Colic, appendicitis, pancreatitis, peptic ulcer disease, bladder distension

Sources: References 22-24 and 88-89.

[a]Visceral organs include the heart, lungs, gastrointestinal tract, pancreas, liver, gallbladder, kidneys, and bladder.

[b]Symptoms and signs of sympathetic (autonomic) nervous system hyperactivity include increased heart rate, blood pressure, and respiratory rate; sweating; pallor; dilated pupils; nausea; vomiting; dry mouth; and increased muscle tension.

in origin.[96] Painful peripheral mononeuropathy and polyneuropathy, deafferentation pain, sympathetically maintained pain, and central pain are subdivisions of these categories.

Neuropathic pain is sometimes called "pathologic" pain because it serves no purpose.[81] A chronic pain state may occur when pathophysiologic changes become independent of the inciting event.[46] Sensitization plays an important role in this process (see I.B.7-8). Although central sensitization is relatively short lived in the absence of continuing noxious input, nerve injury triggers changes in the CNS that can persist indefinitely.[48] Thus, central sensitization explains why neuropathic pain is often disproportionate to the stimulus (e.g., hyperalgesia, allodynia) or occurs when no identifiable stimulus exists (e.g., persistent pain, pain spread). Neuropathic pain may be continuous or episodic and is perceived in many ways (e.g., burning, tingling, prickling, shooting, electric shock-like, jabbing, squeezing, deep aching, spasm, or cold).[97] Table 2 summarizes examples and characteristics of neuropathic pain.

C. Classification of Pain

Although pain classes are not diagnoses, categorizing pain helps guide treatment. Multiple systems for classifying pain exist. These include multidimensional classification systems, such as the IASP Classification of Chronic Pain,[19] and a variety of systems based on a single dimension of the pain experience. Of the latter systems, those

Table 2. Examples and Characteristics of Neuropathic Pain

	Painful Mononeuropathies and Polyneuropathies	Deafferentation Pain	Sympathetically Maintained Pain[a]	Central Pain
Definition	Pain along the distribution of one or multiple peripheral nerve(s) caused by damage to the affected nerve(s)	Pain that is due to a loss of afferent input	Pain that is maintained by sympathetic nervous system activity	Pain caused by a primary lesion or dysfunction of the CNS
Pain characteristics and associated symptoms	Three main types: • Continuous, deep, burning, aching or bruised pain • Paroxysmal lancinating (shock-like) pain • Abnormal skin sensitivity	• Quality: burning, cramping, crushing, aching, stabbing, or shooting • Hyperalgesia • Hyperpathia • Dysesthesia • Other abnormal sensations	• Quality: burning, throbbing, pressing, or shooting • Allodynia • Hyperalgesia • Associated ANS dysregulation and trophic changes[b]	• Quality: burning, numbing, tingling, shooting • Spontaneous and steady or evoked • +/- sensory loss • Allodynia • Hyperalgesia
Sources	• Metabolic disorders (e.g., diabetes) • Toxins (e.g., alcohol chemotherapy agents) • Infection (e.g., HIV, herpes zoster) • Trauma • Compressive (nerve entrapment) • Autoimmune and hereditary diseases	• Damage to a peripheral nerve, ganglion, or plexus • CNS disease or injury (occasional)	• Peripheral nerve damage (e.g., CRPS II) • Sympathetic efferent (motor) innervation • Stimulation of nerves by circulating catecholamines	• Ischemia (e.g., stroke) • Tumors • Trauma (e.g., spinal cord injury) • Syrinx • Demyelination
Clinical examples	• Diabetic neuropathy • Alcoholic neuropathy • Postherpetic neuralgia • Carpal tunnel syndrome	• Phantom limb pain • Post-mastectomy pain	• CRPS • Phantom limb pain • Postherpetic neuralgia • Some metabolic neuropathies	• Post-stroke pain • Some cancer pain • Pain associated with multiple sclerosis

Sources: References 22-23, 87, and 97a-97d.

[a]Sympathetically maintained pain is a pain mechanism, not a diagnosis. It is associated with several types of pain, but it also may exist as a single entity.[97c]

[b]Focal autonomic dysregulation can manifest with signs and symptoms such as swelling, pallor, erythema (redness), sweating, and temperature changes. Trophic changes include thinning of the skin, abnormal hair or nail growth, and bone changes.

ANS: autonomic nervous system; CNS: central nervous system; CRPS: complex regional pain syndrome types I and II; CRPS II: complex regional pain syndrome type II; HIV: human immunodeficiency virus.

based on pain duration (i.e., acute vs. chronic pain) and underlying pathophysiology (i.e., nociceptive vs. neuropathic pain) are used most often (see I.B.9-10).

This section of the monograph explores the distinction between acute and chronic pain. It also reviews elements of a mixed pain classification system in which pain is categorized as acute pain, cancer pain, or chronic noncancer pain (CNCP).

1. Acute Pain

Acute pain was once defined simply in terms of duration. It is now viewed as a "complex, unpleasant experience with emotional and cognitive, as well as sensory, features that occur in response to tissue trauma."[22] In contrast to chronic pain, relatively high levels of pathology usually accompany acute pain and the pain resolves with healing of the underlying injury. Acute pain is usually nociceptive, but may be neuropathic. Common sources of acute pain include trauma, surgery, labor, medical procedures, and acute disease states. Table 3 summarizes its key features.

Acute pain serves an important biological function, as it warns of the potential for or extent of injury. A host of protective reflexes (e.g., withdrawal of a damaged limb, muscle spasm, autonomic responses) often accompany it. However, the "stress hormone response" prompted by acute injury also can have adverse physiologic and emotional effects (see I.D.3).[13] Even brief intervals of painful stimulation can induce suffering, neuronal remodeling, and chronic pain;[10] associated behaviors (e.g., bracing, abnormal postures, excessive reclining) may further contribute to the development of chronic pain. Therefore, increasing attention is being focused on the aggressive prevention and treatment of acute pain to reduce complications, including progression to chronic pain states.[88]

2. Chronic Pain

Chronic pain was once defined as pain that extends 3 or 6 months beyond onset or beyond the expected period of healing.[98] However, new definitions differentiate chronic pain from acute pain based on more than just time (Table 3). Chronic pain is now recognized as pain that extends beyond the period of healing, with levels of identified pathology that often are low and insufficient to explain the presence and/or extent of the pain.[99] Chronic pain is also defined as a persistent pain that "disrupts sleep and normal living, ceases to serve a protective

Table 3. Key Features of Pain Types and Syndromes

Type of Pain	Features
Acute pain	Pain usually concordant with degree of tissue damage, which remits with resolution of the injury Reflects activation of nociceptors and/or sensitized central neurons Often associated with ANS and other protective reflex responses (e.g., muscle spasm, "splinting")
Chronic pain	Low levels of identified underlying pathology that do not explain the presence and/or extent of the pain Perpetuated by factors remote from the cause Continuous or intermittent with or without acute exacerbations Symptoms of ANS hyperactivity less common Irritability, social withdrawal, depressed mood and vegetative symptoms (e.g., changes in sleep, appetite, libido), disruption of work, and social relationships
Cancer pain	Strong relationship between tissue pathology and levels of pain Limited time frame that permits aggressive pain management Rarely involves medical-legal or disability issues
CNCP	Weak relationship between tissue pathology and pain levels Prolonged, potentially life-long, pain May involve medical, legal, disability issues/conflicts, work or relationship problems, physical deconditioning, psychological symptoms (see chronic pain above) May progress to CPS
CPS	Preoccupation with somatic functioning Lifestyle centered on seeking immediate pain relief, with excessive, nonproductive, and often harmful use of health care services Repeated attempts to obtain pain-related financial compensation (e.g., Social Security, Veterans' benefits) Numerous symptoms and signs of psychosocial dysfunction that the patient attributes to the pain (e.g., anger, depression, anxiety, substance abuse, disrupted work or personal relationships)

Sources: References 88 and 98-100.
ANS: autonomic nervous system; CNCP: chronic noncancer pain; CPS: chronic pain syndrome; VA: Veterans Administration.

function, and instead degrades health and functional capability."[101] Thus, unlike acute pain, chronic pain serves no adaptive purpose.

Chronic pain may be nociceptive, neuropathic, or both and caused by injury (e.g., trauma, surgery), malignant conditions, or a variety of chronic non-life-threatening conditions (e.g., arthritis, fibromyalgia, neuropathy). In some cases, chronic pain exists de novo with no apparent cause. Although injury often initiates chronic pain, factors pathogenetically and physically remote from its cause may perpetuate it.[98] Environmental and affective factors also can exacerbate and perpetuate chronic pain, leading to disability and maladaptive behavior.

3. Cancer Pain

Pain associated with potentially life-threatening conditions such as cancer is often called "malignant pain" or "cancer pain." However, there is movement toward the use of new terms such as "pain associated with human immunodeficiency virus (HIV) infection" or "pain associated with cancer." (The term "cancer pain" is used in this monograph for the sake of brevity.) Cancer pain includes pain caused by the disease itself (e.g., tumor invasion of tissue, compression or infiltration of nerves or blood vessels, organ obstruction, infection, inflammation) and/or painful diagnostic procedures or treatments (e.g., biopsy, postoperative pain, toxicities from chemotherapy or radiation treatment).[102]

There are several reasons why some experts feel that cancer pain merits a discrete category. First, its acute and chronic components and multiple etiologies make it difficult to classify based on duration or pathology alone. Second, cancer pain differs from chronic noncancer pain (CNCP) in some significant ways (e.g., time frame, levels of pathology, treatment strategies) (Table 3).[99] However, there is little evidence to support a distinction between these pain types based on underlying neural processes. Therefore, many pain experts categorize cancer pain as acute or chronic pain.[98]

4. Chronic Noncancer Pain

A subtype of chronic pain is CNCP, which refers to persistent pain not associated with cancer. In contrast to patients with chronic cancer pain, patients with CNCP often report pain levels that only weakly correspond to identifiable levels of tissue pathology and/or respond poorly to standard treatments.[99-100] As CNCP may last for many years, some consider use of the traditional term for such pain, "chronic nonmalignant pain," inappropriate. Thus, there is movement toward use of alternate terms such as "chronic noncancer pain" and "chronic noncancer-related pain."

Causes of CNCP include acute injury that has proceeded to chronic pain (e.g., whiplash) and various chronic conditions (Table 4). In some cases, there is no discernable cause, and the pain is considered the disease. CNCP can affect virtually any body system or region, and pain severity ranges from mild to excruciating. Some types of CNCP have well-defined characteristics and patterns, whereas others do not. Neuropathic and myofascial CNCP can be particularly hard to diagnose, as they may occur in the absence of a known injury or disease process.[100]

Because of its chronicity and impact on daily activities, patients with CNCP may experience vocational, interpersonal, and/or psychological problems (Table 3).[15] If the symptoms of CNCP consume the attention of and incapacitate the patient, he or she may suffer from a psychosocial disorder known as "chronic pain syndrome" (CPS) (Table 3).[100] The pain experienced by these patients is real, and not all patients with CNCP develop this syndrome. Appropriate management of both CNCP and CPS requires an

Table 4. Examples of Chronic Noncancer Pain

- Osteoarthritis
- Low back pain
- Myofascial pain
- Fibromyalgia
- Headaches (e.g., migraine[a], tension-type, cluster)
- "Central pain" (e.g., spinal cord injury, stroke, MS)
- Chronic abdominal pain (e.g., chronic pancreatitis, chronic PUD, IBS)
- Sickle cell disease[a]
- CRPS, Types I and II
- Phantom limb pain
- Peripheral neuropathy
- Neuralgia (e.g., post-herpetic, trigeminal)

Sources: References 99 and 100.

[a]Migraines and sickle cell disease may be more accurately classified as intermittent pain but are treated as chronic noncancer pain for purposes of this discussion.
CRPS: complex regional pain syndrome; IBS: Irritable bowel syndrome; MS: multiple sclerosis; PUD: peptic ulcer.

interdisciplinary approach that addresses the complex interaction of physical, psychological, and social factors that contribute to the ongoing pain.

D. Prevalence, Consequences, and Costs of Pain

Pain is common, and inadequately managed pain is associated with many adverse consequences. This section of the monograph reviews epidemiological data, evidence that pain is undertreated, and consequences of inadequately managed pain. These consequences affect patients, their families, and society as a whole and can be broadly categorized as physiological, psychosocial (quality of life), and financial.

1. What Is the Size and Scope of Pain As A Health Care Problem?

Acute pain is the most common reason why patients seek medical attention.[88] Common reasons for visits to health care professionals include acute pain (e.g., musculoskeletal pain, gastrointestinal pain, chest pain, headache) and injuries (e.g., fractures, sprains, lacerations).[103] Chronic pain is also a problem of epidemic proportions. About 50 million of the estimated 75 million Americans who live with "serious pain" suffer from chronic pain.[104] Many have been living with their pain for more than 5 years and experience pain almost 6 days a week.[14] A survey of self-help organization members suggested that back and neck pain, myofascial pain/fibromyalgia, headache, arthritis pain, and neuropathic pain are the most common types of CNCP.[105] Low back pain, arthritis, and migraine headache alone account for pain in tens of millions of Americans.[88]

2. What Evidence Suggests That Pain Is Undertreated?

In 1992, the AHCPR developed a CPG for acute pain management, in part due to mounting reports of inadequate postoperative pain control.[13] Clinical surveys indicated that routine orders for as-needed intramuscular (IM) injections of opioids failed to relieve pain in about half of all postoperative patients (e.g., Marks and Sachar,[106] Donovan et al.,[107] Oden[108]). This finding prompted recommendations including the scheduled administration of pain medications via other routes. A national survey of perioperative pain in hospitalized patients recently assessed adherence to these and other (American Society of Anesthesiologists) CPGs.[109] Although overall guideline adherence was excellent, frequent IM administration of opioids and infrequent use of nonpharmacologic pain management methods were important exceptions.

Results of other 1990s studies (e.g., Abbott et al.,[110] Gu and Belgrade,[111] Ward and Gordon,[112] Warfield and Kahn,[113] Drayer et al.[114]) contribute to concerns about the management of acute pain. In one study of pain management in hospitalized patients, 61% of the 217 patients interviewed reported pain ratings of 7 to 10 (on a scale from 0 for no pain and 10 for the worst imaginable pain) within the preceding 24 hours.[112] Forty-nine percent reported a current pain level between 4 and 10, and this was after analgesic administration in 20%. A study of the adequacy of analgesia in an urban emergency department produced some disturbing results. Hispanic patients with long-bone fractures were half as likely as non-Hispanic white patients to receive pain medication.[115]

A 1998 survey of a random cross-section of U.S. households suggests that CNCP also is undertreated.[14] Of 805 adults interviewed, 70% reported sufficient control of moderate pain. However, this percentage decreased to 51% in patients with severe pain and to 39% in those with very severe pain. Results from a 2001 survey suggest that most individuals with severe CNCP still do not have their pain under control.[14] Of those who do, it took almost half of them a year to achieve adequate pain control.[14]

Undertreatment of cancer pain also is well documented. A landmark study involved 1308 cancer outpatients at 54 treatment sites.[116] Approximately two-thirds (67%) of the patients interviewed reported pain sufficient to require daily analgesics, and 36% reported that the pain limited their ability to function. However, only 42% of those with pain reported receiving sufficient pain relief. Data from more recent studies (e.g., Zhukovsky et al.,[117] Cleeland et al.,[118] Anderson et al.,[119] Wolf et al.,[120] Weiss et al.[121]) suggest that pain associated with terminal illnesses, including cancer, is still undertreated. Elderly, female, minority, and pediatric patients

are at greatest risk for inadequate management of cancer pain.[120,122]

3. What Are the Consequences and Costs of Undertreatment of Pain?

a. Physiological consequences

As discussed in Section I.C.1, acute tissue injury triggers physiological "stress" responses intended to protect the body. Yet these responses can have adverse effects if allowed to persist unchecked. Table 5 summarizes some of the adverse physiological consequences of inadequately controlled postinjury and postoperative pain (e.g., pneumonia, blood clots, infection, shock). Very young, very old, and frail patients are at greatest risk for such complications.[13] In one study of neonates who underwent cardiac surgery, patients who received "light" versus "deep" anesthesia and postoperative analgesia had higher mortality rates.[123]

Another key adverse effect of poorly controlled acute pain is progression to chronic pain.[124-125] Some chronic neuropathic pain (e.g., postmastectomy pain, postthoracotomy pain, phantom limb pain) results, in part, from a lack of aggressive pain management and/or early rehabilitation following surgery.[126-127] Inadequate control of pain associated with acute herpes zoster (shingles) may increase the likelihood of subsequent postherpetic neuralgia.[128] One study showed that pain levels in patients hospitalized for serious conditions (e.g., chronic obstructive pulmonary disease, liver failure, cancer) determined future pain levels.[129] Undertreated pain early in life is associated with pain later in life.[130-131]

b. Quality of life

Inadequate control of pain interferes with the pain sufferer's ability to carry out activities of daily living (e.g., work, relationships, hobbies, sex).[14] It also has adverse psychological consequences. Patients with inadequately managed pain may experience anxiety, fear, anger, depression, or cognitive dysfunction,[15] and family members report varying levels of helplessness, frustration, and "heartbreak."[132]

These consequences are especially likely to occur in patients with chronic pain. These individuals report impairments on multiple measures of physical, social, and psychological well-being, and many experience psychological symptoms (e.g., depression, anxiety) that adversely influ-

Table 5. Examples of Physiological Consequences of Unrelieved Pain

Functional Domain	Stress Responses to Pain	Examples of Clinical Manifestations
Endocrine/metabolic	Altered release of multiple hormones (e.g., ACTH, cortisol, catecholamines, insulin) with associated metabolic disturbances	Weight loss Fever Increased respiratory and heart rate Shock
Cardiovascular	Increased heart rate Increased vascular resistance Increased blood pressure Increased myocardial oxygen demand Hypercoagulation	Unstable angina (chest pain) Myocardial infarction (heart attack) Deep vein thrombosis (blood clot)
Respiratory	Decreased air flow due to involuntary (reflex muscle spasm) and voluntary ("splinting") mechanisms that limit respiratory effort	Atelectasis Pneumonia
Gastrointestinal	Decreased rate of gastric emptying Decreased intestinal motility	Delayed gastric emptying, constipation, anorexia, ileus[a]
Musculoskeletal	Muscle spasm Impaired muscle mobility and function	Immobility Weakness Fatigue
Immune	Impaired immune function	Infection
Genitourinary	Abnormal release of hormones that affect urine output, fluid volume, and electrolyte balance	Decreased urine output Hypertension (fluid retention) Electrolyte disturbances

Sources: References 13 and 23.

[a]Mechanical, dynamic, or adynamic obstruction of bowel often manifests as colicky pain, distension, vomiting, and absence of the passage of stool.

ACTH: adrenocorticotrophic hormone.

ence health care.[15] Left unchecked, these symptoms can contribute to more serious consequences. In one study, about half of the patients with CNCP reported that they had considered suicide despite the availability of resources and coping strategies.[105]

c. Financial consequences

Pain costs Americans an estimated $100 billion each year.[4,133] Patients, families, health care organizations, and society bear this financial burden. Patients with chronic pain are five times as likely as those without chronic pain to use health care services.[15] In addition, medical complications associated with inadequately controlled acute pain can increase length of stay, rehospitalization rates, and outpatient visits.[135] Results from some studies (e.g., Burke et al.[h,135]) suggest that adequate management of acute (postoperative) pain can reduce length of stay and costs.

Pain is also costly in terms of lost productivity and income. It is a leading cause of medically related work absenteeism and results in more than 50 million lost work days per year in the United States.[2,136] About 25% of the population in industrialized nations suffers from chronic pain of sufficient severity that they miss days of work.[137] Individuals with chronic pain often face long-term or permanent unemployment or underemployment.

E. Barriers to the Appropriate Assessment and Management of Pain

The undertreatment of pain reflects barriers to both assessment and management. These barriers can be broadly categorized as those attributable to the health care system, clinicians, patients and families, laws and regulations, and society.[134,138-139] Collectively, these barriers contribute to a failure to assess pain, to accept the patient's self-report of pain, and/or to take appropriate action.[140]

[h]Burke et al. compared resource utilization and costs between groups of patients who did or did not receive ketorolac for management of postoperative pain.[135]

1. Barriers Within the Health Care System

Systems barriers to pain assessment and management include an absence of clearly articulated practice standards and failure of the system to make pain relief a priority.[134,141-142] For example, some health care organizations fail to adopt a standard pain assessment tool or to provide staff with sufficient time and/or chart space for documenting pain-related information.[134] Others fail to provide clinicians with practical tools and training to improve pain management such as CPGs, algorithms, protocols, and computer help screens. However, the greatest systems barrier to appropriate pain management is a lack of accountability for pain management practices. Institutions and health care organizations must implement means of holding clinicians accountable for adequate pain assessment and management (e.g., chart audits of pain documentation, pain competencies in staff orientation and performance evaluations, formal reviews for critical incidents) to ensure effective pain management.[134]

Recent changes in the health care system (e.g., growth of managed care, shift from inpatient to outpatient treatment settings, new reimbursement policies) also have introduced barriers to pain management. Patient care is more fragmented; thus, the risk of poor coordination of care across treatment settings is increased.[141,143] The use of gatekeepers and formularies by managed care organizations may impede access to pain specialists, comprehensive pain management facilities, and certain analgesic therapies.[141,143] In addition, inconsistent reimbursement policies for pain treatment, or concern that aggressive treatment will increase costs, can lead to inadequate treatment of pain.[144]

2. Health Care Professional Barriers

Clinicians' attitudes, beliefs, and behaviors contribute to the undertreatment of pain. For example, some clinicians do not view pain relief as important and/or do not want to "waste time" assessing pain.[141] Others refuse to accept that the patient's self-report is the most reliable indicator of pain. Studies have shown that lack of assessment, underassessment, and a disparity between the clinician's and the patient's ratings of pain intensity are major causes of inadequately controlled pain (e.g., Donovan et al.,[107] Drayer et al.,[114] Grossman et al.,[145] Gu and Belgrade,[111] Paice et al.,[146] Von Roenn et al.[147]).

Inappropriate or exaggerated concerns and inadequate or inaccurate clinical knowledge also limit clinicians' abilities to appropriately manage pain.[139,141,144] Concerns often relate to aspects of pharmacologic treatment such as regulatory scrutiny, analgesic side effects, and iatrogenic addiction (see I.E.5). Problems with clinical knowledge include inadequate understanding of pharmacology and misconceptions about pain (Table 6).

3. Patient and Family Barriers

Whereas poor clinician-patient communication may reflect deficits in the clinician's skills, certain patient characteristics (e.g., age, language, cognitive abilities, coexisting physical or psychological illness, cultural traditions) may impair a patient's ability to communicate.[13] Alternatively, patients may be reluctant to report pain to clinicians due to low expectations of obtaining relief, stoicism, fears, or concerns about what the pain means (e.g., worsening disease, death), analgesic side effects, or addiction.[141] In a recent survey of terminally ill patients, whereas half experienced moderate to severe pain, only 30% wanted additional pain treatment.[121] Reasons the patients offered for declining additional therapy included fear of addiction, dislike of mental or physical drug side effects, and not wanting to take more pills or injections.

Other patient and family factors that contribute to the undertreatment of pain include financial barriers (e.g., lack of health insurance, high cost of certain medications) and even poor adherence to treatment regimens.[14,141] Limited data suggest that patients do not always take analgesics as prescribed.[148-150] In addition, some patients with chronic pain do not seek medical attention. A recent survey of individuals with CNCP suggested that, while most chronic pain sufferers have visited a doctor at some point, almost 40% are not currently under the care of a physician.[14] Difficulty in locating a clinician who could effectively manage their pain was a commonly cited reason.

Table 6. Common Misconceptions About Pain

The incorrect beliefs that:

- Physical or behavioral signs of pain (e.g., abnormal vital signs, grimacing, limping) are more reliable indicators of pain than patient self-report.
- Elderly or cognitively impaired patients cannot use pain intensity rating scales.
- Pain does not exist in the absence of physical or behavioral signs or detectable tissue damage.
- Pain without an obvious physical cause, or that is more severe than expected based on findings, is usually psychogenic.
- Comparable stimuli produce the same level of pain in all individuals (i.e., a uniform pain threshold exists).
- Prior experience with pain teaches a person to be more tolerant of pain.
- Analgesics should be withheld until the cause of the pain is established.
- Noncancer pain is not as severe as cancer pain.
- Patients who are knowledgeable about pain medications, are frequent emergency department patrons, or have been taking opioids for a long time are necessarily addicts or "drug seekers."
- Use of opioids in patients with pain will cause them to become addicted.
- Patients who respond to a placebo drug are malingering.
- Neonates, infants, and young children have decreased pain sensation.

Sources: References 13 and 140.

4. Legal and Societal Barriers

Legal and societal issues also contribute to the undertreatment of pain. The former include restrictive laws or regulations about the prescribing of controlled substances as well as confusion about the appropriate role of opioids in pain treatment.[141,151] Societal issues that contribute to the undertreatment of pain include drug abuse programs and erroneous beliefs about tolerance, physical dependence, and addiction (see I.E.5). For example, some clinicians incorrectly assume that exposure to an addictive drug usually results in addiction.

5. Tolerance, Physical Dependence, and Addiction

a. Definitions

Many medications, including opioids, play important roles in pain management. However, concerns about their potential misuse and misunderstanding of the nature and risk of addiction limit their appropriate use.[152] Disparate definitions of tolerance, physical dependence, and addiction contribute to this problem. Therefore, the American Society of Addiction Medicine (ASAM), the American Academy of Pain

Medicine (AAPM), and the American Pain Society (APS) recently recommended use of the following definitions:[152]

- *Tolerance:* "Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time."
- *Physical Dependence:* "Physical dependence is a state of adaptation that often includes tolerance and is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist."
- *Addiction:* "Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."

Although other definitions exist (e.g., DSM-IV), experts consider these terms the most applicable to pain management. A related term, pseudoaddiction, refers to patient behaviors that may occur when pain is undertreated, including increased focus on obtaining medications ("drug seeking"), "clock watching," and even illicit drug use or deception.[153] Pseudoaddiction can be distinguished from true addiction because such behaviors resolve with effective pain management.[152]

b. Etiology, issues, and concerns

Many medications produce tolerance and physical dependence, and some (e.g., opioids, sedatives, stimulants, anxiolytics, some muscle relaxants) may cause addiction in vulnerable individuals.[152] Most experts agree that patients who undergo prolonged opioid therapy usually develop physical dependence but do not develop addictive disorders.[152] In general, patients in pain do not become addicted to opioids. Although the actual risk of addiction is unknown,[152] it is thought to be quite low. A recent study of opioid analgesic use revealed "low and stable" abuse of opioids between 1990 and 1996 despite significant increases in opioids prescribed.[154] Drug exposure appears to be only one etiologic factor in the development of addiction,[152] and genetic, social, and psychologic factors may be more significant determinants.[155-158]

Fear of causing addiction (i.e., iatrogenic addiction), particularly with opioid use, is a major barrier to appropriate pain management.[8,159-162] This fear sometimes reflects a lack of understanding of the risk of addiction with therapeutic drug use. Although studies suggest that the risk of iatrogenic addiction is quite low (e.g., Perry and Heidrich,[163] Zenz et al.[164]), surveys indicate that clinicians often overestimate this risk.[165-167] Alternatively, clinicians may be reluctant to prescribe an opioid because they have witnessed the devastation that addiction can cause in a patient's life.

Clinicians are also often reluctant to prescribe opioids due to concerns about licensing issues, peer review, state disciplinary action, and even legal prosecution (i.e., for over-prescribing, or under-prescribing, controlled substances).[104] The Federation of State Medical Boards of the United States (FSMB) acknowledges such potential in their 1998 "Model Guidelines for the Use of Controlled Substances for the Treatment of Pain."[160] These guidelines attribute inadequate pain control to three major factors:

- Physicians' lack of knowledge about pain management,
- Inadequate understanding of addiction, and
- Fear of investigation or sanction by federal, state, and local regulatory agencies.[160]

These guidelines acknowledge that: "controlled substances, including opioid analgesics, may be essential in the treatment of acute pain due to trauma or surgery and chronic pain, whether due to cancer or non-cancer origins."[160] They assert that physicians should not fear disciplinary action for prescribing, dispensing, or administering controlled substances for a legitimate medical purpose (including pain) in the usual course of professional practice.[160] However, they also state that "all such prescribing must be based on clear documentation of unrelieved pain and in compliance with applicable state or federal law."[160] These guidelines and other information about regulatory issues are located at www.fsmb.org/policy.htm and http://www.med-sch.wisc.edu/painpolicy, respectively, on the World Wide Web. The latter URL also contains up-to-date information on specific state laws and regulations.

Section II:

Assessment of Pain

A. Initial Assessment of Pain

Assessment is an essential, but challenging, component of any pain management plan. Pain is subjective, so no satisfactory objective measures of pain exist. Pain is also multidimensional, so the clinician must consider multiple aspects (sensory, affective, cognitive) of the pain experience. Finally, the nature of the assessment varies with multiple factors (e.g., purpose of the assessment, the setting, patient population, clinician), so no single approach is appropriate for all patients or settings.

This section reviews some core principles of pain assessment and management to help guide this process. It then explores approaches that clinicians can use in the initial assessment of pain (i.e., patient history, physical examination, diagnostic studies). Subsequent discussions explore tools that facilitate assessment and address the reassessment of pain.

1. Overcoming Barriers to Assessment

Underassessment of pain is a major cause of inadequate pain management (see I.E). In fact, the most common reason for the undertreatment of pain in U.S. hospitals is the failure of clinicians to assess pain and pain relief.[1] This situation has prompted recent efforts to raise clinicians' awareness of the importance of pain assessment. In 1996, the American Pain Society (APS) introduced the phrase "pain as the 5th vital sign."[a,2] This initiative emphasizes that pain assessment is as important as assessment of the standard four vital signs and that clinicians need to take action when patients report pain.[1] The Veterans Health Administration recognized the value of such an approach and included pain as the 5th Vital Sign in their national pain management strategy.[3]

In addition to these efforts, the Joint Commission on Accreditation of Healthcare Organization (JCAHO) recently introduced standards for pain assessment and management relevant to multiple health care disciplines and settings (see V.B.1). These standards stress patients' rights to appropriate assessment and management of pain (JCAHO Standard RI 1.2.8, 2000) and emphasize that pain should be assessed in all patients (JCAHO Standard PE1.4, 2000).[4] Multiple additional clinical practice guidelines (CPGs) for pain management have emerged since the first guideline for pain management in 1992 (see V). Thus, the means for improved pain assessment and management are readily available. Successful pain management depends, in part, on clinician adherence to such standards and guidelines and commitment to some core principles of pain assessment and management (Table 7).

[a]The Pain as the 5th Vital Sign initiative is a concept, not a guide, for pain assessment. Whereas assessing pain with each assessment of the standard four vital signs is appropriate in some clinical situations, more or less frequent assessment may be appropriate in others.

2. Goals and Elements of the Initial Assessment

Important goals of the initial assessment of pain include establishing rapport with the patient and providing an overview of the assessment process.[8] These processes help to engage the patient, foster appropriate treatment expectations, and promote a coordinated approach to management. The clinician's primary objective is to obtain information that will help identify

Table 7. Core Principles of Pain Assessment and Management

- Patients have the right to appropriate assessment and management of pain (JCAHO Standard RI 1.2.8, 2000). Pain (should be) is assessed in all patients (JCAHO Standard PE1.4, 2000).
- Pain is always subjective.[1] Therefore, the patient's self-report of pain is the single most reliable indicator of pain.[5] A clinician needs to accept and respect this self-report, absent clear reasons for doubt.
- Physiological and behavioral (objective) signs of pain (e.g., tachycardia, grimacing) are neither sensitive nor specific for pain.[5] Such observations should not replace patient self-report unless the patient is unable to communicate.[5]
- Assessment approaches, including tools, must be appropriate for the patient population. Special considerations are needed for patients with difficulty communicating. Family members should be included in the assessment process, when possible.
- Pain can exist even when no physical cause can be found. Thus, pain without an identifiable cause should not be routinely attributed to psychological causes.
- Different patients experience different levels of pain in response to comparable stimuli. That is, a uniform pain threshold does not exist.
- Pain tolerance varies among and within individuals depending on factors including heredity, energy level, coping skills, and prior experiences with pain.
- Patients with chronic pain may be more sensitive to pain and other stimuli.
- Unrelieved pain has adverse physical and psychological consequences. Therefore, clinicians should encourage the reporting of pain by patients who are reluctant to discuss pain, deny pain when it is likely present, or fail to follow through on prescribed treatments (JCAHO standard PE1.4, 2000).
- Pain is an unpleasant sensory and emotional experience, so assessment should address physical and psychological aspects of pain.

Sources: References 1 and 4-7.

the cause of the pain and guide management. A patient history, physical examination, and appropriate diagnostic studies are typically conducted for this purpose.

a. Patient history

The patient's self-report of pain is the most reliable indicator of pain.[5] Physiological and behavioral (objective) signs of pain (e.g., tachycardia, grimacing) are neither sensitive nor specific for pain and should not replace patient self-report unless the patient is unable to communicate.[5] Therefore, talking to patients and asking them about their pain (i.e., obtaining a "pain history") is integral to pain assessment.

The pain history usually is obtained as part of the patient history, which includes the patient's past medical history, medications, habits (e.g., smoking, alcohol intake), family history, and psychosocial history. Obtaining a comprehensive history provides many potential benefits, including improved management, fewer treatment side effects, improved function and quality of life, and better use of health care resources.[9]

The manner in which information is elicited from the patient is important. Ideally, the clinician should afford ample time, let the patient tell the story in his or her own words, and ask open-ended questions. Information to be elicited during the initial assessment of pain includes (see Table 8):

- Characteristics of the pain (e.g., duration, location, intensity, quality, exacerbating/alleviating factors)
- Present and past pain management strategies and their outcomes
- Past and present medical problems that may

Table 8. Information From the Patient History

Parameter	Information To Be Obtained	Sample Questions
Pain characteristics	Onset and duration	When did the pain begin?
	Location(s)	Where does it hurt? (Use diagram, when possible.)
	Quality	What does the pain feel like?
	Intensity (severity)	How severe is the pain right now? (Use numeric rating scale to obtain score, when possible.)
	Associated symptoms	
	Exacerbating or alleviating factors	What increases or decreases the pain?
Management strategies	Past and current: • Medications ("natural," nonprescription, and prescription) • Nonpharmacologic treatments • Coping strategies (e.g., prayer, distraction)	What methods have you used to manage the pain? What methods have worked?
Relevant medical history	Prior illnesses (including psychiatric illnesses and chemical dependence), surgeries, and accidents	How is your general health?
	Coexisting acute or chronic illnesses	Have you had any problems with pain in the past?
	Prior problems with pain and treatment outcomes	If so, how did you manage the pain?
Relevant family history	Health of family members	How is the health of your family?
	Family history of chronic pain or illnesses	Do any family members have problems with pain?
Psychosocial history	Past or current: • Developmental, marital, or vocational problems • Stressors or depressive symptoms • "Reinforcers" of the pain (e.g., compensation-litigation issues)	Are there any recent sources of increased stress? How has the pain affected your mood?
Impact of the pain on the patient's daily life	Impact of the pain on the patient's: • Work • Other daily activities (e.g., chores, hobbies) • Personal relationships • Sleep, appetite, emotional state	How has the pain affected your work and relationships with others? How is your sleep? How is your appetite?
Patient's expectations and goals	Expectations and goals for pain management in regard to pain intensity, daily activities, and quality of life	What are your goals for treatment?

Sources: References 5 and 7-8.

influence the pain and/or its management
- Relevant family history
- Current and past psychosocial issues or factors that may influence the pain and its management
- The impact of the pain on the patient's daily life and functioning
- The patient's and family's knowledge of, expectations about, and goals for pain management.

Careful characterization of the pain facilitates diagnosis and treatment (see Table 9). Assessment tools (e.g., rating scales, questionnaires) play an important role in this process (see II.B). Both the choice of tool and the general approach to assessment should reflect the needs of the patient.

The assessment of pain in some patients warrants special consideration. Tables 10 and 11 summarize approaches to assessment in patients with impaired ability to communicate. Tables 12 and 13 review recommended pre- and post-operative assessment and management methods for perioperative pain, including pain after the surgery (postoperative pain). Patient education about these methods is a key element of the initial assessment of a surgical patient. As unrelieved pain has adverse physical and psychological consequences, clinicians should encourage the reporting of pain by patients who are reluctant to discuss pain or who deny pain that is likely to be present (JCAHO standard PE1.4, 2000).

The initial assessment of a patient with chronic pain, especially chronic noncancer pain (CNCP), also warrants special consideration. Associated neural remodeling (central sensitization) means that the pain may exist without an apparent physical cause (see I.B.8). In such cases, the clinician needs to avoid attributing the pain to psychological causes and to accept and respect the patient's self-report of pain.[5] Other clinicians often have seen and/or treated patients with CNCP. Therefore, past medical records, test results, and treatment histories need to be obtained. Given the link between chronic pain and

Table 9. Characteristics of Pain Types

Characteristic	Pain Types and Examples
Location and distribution	Localized pain: pain confined to site of origin (e.g., cutaneous pain, some visceral pain, arthritis, tendonitis)
	Referred pain: pain that is referred to a distant structure (e.g., visceral pain such as angina, pancreatitis, appendicitis, acute cholecystitis)
	Projected (transmitted) pain: pain transferred along the course of a nerve with a segmental distribution (e.g., herpes zoster) or a peripheral distribution (e.g., trigeminal neuralgia)
	Dermatomal patterns: peripheral neuropathic pain
	Nondermatomal: central neuropathic pain, fibromyalgia
	No recognizable pattern: complex regional pain syndrome
Duration and periodicity	Brief flash: quick pain such as a needle stick
	Rhythmic pulses: pulsating pain such as a migraine or toothache
	Longer-duration rhythmic phase: intestinal colic
	Plateau pain: pain that rises gradually or suddenly to a plateau where it remains for a prolonged period until resolution (e.g., angina)
	Paroxysmal: neuropathic pain
	Continuously fluctuating pain: musculoskeletal pain
Quality	Superficial somatic (cutaneous) pain: sharp pricking or burning
	Deep somatic pain: dull or aching
	Visceral pain: dull aching or cramping
	Neuropathic pain: burning, shock-like, lancinating, jabbing, squeezing, aching
Associated signs and symptoms	Visceral pain: "sickening feeling," nausea, vomiting, autonomic symptoms
	Neuropathic pain: hyperalgesia, allodynia
	Complex regional pain syndrome: hyperalgesia, hyperesthesia, allodynia, autonomic changes, and trophic changes (skin, hair, nail changes)

Sources: References 8 and 10.

Table 10. Assessment of Patients With Barriers to Communication

Patient Populations
- Infants and children
- Individuals of advanced age (e.g., older than 85 years)
- Adults with emotional or cognitive disturbances
- Patients with cultural, educational, or language barriers to communication
- Intubated patients
- Patients who are seriously ill

General Approach
- Allow sufficient time for the assessment.
- Give patient the opportunity to use a rating scale or other tool appropriate for that population.
- Use indicators of pain according to the following hierarchy of importance:
  - Patient self-report
  - Pathological conditions or procedures known to be painful
  - Pain-related behaviors (e.g., grimacing, restlessness, vocalization)
  - Reports of pain by family members or caretakers
  - Physiological measures (vital signs).
- Rely on behavioral or objective indicators of pain (e.g., vital signs) only when no suitable alternative exists.

Sources: References 5, 7, and 11.

Table 11. Assessment Challenges and Approaches in Special Populations

Population	Challenges	Approaches
Elderly	Under-reporting of discomfort due to fear, cultural factors, stoicism Impairments (e.g., hearing, vision, comprehension, verbal skills) may limit ability to communicate Difficulty with visually oriented or complex assessment tools	Avoid time pressure in assessment Evaluate for impairments that limit ability to communicate Use tools that the elderly find easy to use (e.g., FPS[a]) Be aware of changes in various parameters in elderly patients (impaired ADLs, social function, walking) that may be indicative of unrelieved pain
Infants and children	Difficulty communicating (e.g., pre-verbal) Difficulty discriminating between anxiety and pain intensity	Select an approach that is consistent with the patient's developmental stage For infants, rely on indicators such as crying and reflex withdrawal In toddlers, watch for pursed lips, wide opening of eyes, rocking, rubbing, defensive behavior (e.g., biting, hitting, kicking, running away) Use age-appropriate assessment tools for children 3 years or older (e.g., Oucher picture scale, FPS, "thermometer" NRS[a])
Patients of different cultural or language backgrounds	Different languages Different behavioral responses to pain Different treatment preferences	Use words such as "pain," "hurt," and "ache" Use assessment tools in appropriate language Provide patient education materials in native language, when possible

Sources: References 7 and 11-16.

[a]See Table 17 for information about FPS and NRS.

ADLs: activities of daily living; FPS: Faces Pain Scale; NRS: numeric rating scale.

depression, the impact of the pain on the patient's mood, satisfaction, quality of life, and cognitive functioning also requires thorough exploration. Key elements of this evaluation include a more comprehensive psychosocial assessment, psychiatric evaluation, psychometric testing (as appropriate), and assessment of function and any disability (see Table 14).[9,18]

b. Physical examination

The initial assessment of a patient with pain includes a physical examination. The clinician uses this examination to help identify the underlying cause(s) of the pain and reassure the patient that his or her complaints of pain are taken seriously.[8] During this examination, the clinician appraises the patient's general physical condition, with special attention to the musculoskeletal and neurological systems and site(s) of pain (see Table 15). The clinician also may evaluate the effect of various physical factors (e.g., motion, applied heat or cold, deep breathing, changes in position) on the pain and/or performance measures of physical function (e.g., range of motion, ability of patient to carry out activities of daily living).

Patients with some types of pain (e.g., chronic and/or neuropathic pain) require more extensive neurological and musculoskeletal assessment. For example, a clinician may need to use a dermatome map to determine the origin of neuropathic pain or perform a formal assessment of disability in a patient who is applying for disability benefits.

c. Diagnostic studies

The need for and type of diagnostic studies are determined by characteristics of the pain and suspected underlying condition. Appropriately selected tests can lead to accurate diagnosis and improve outcomes (e.g., reduce pain and adverse effects of therapy, improve function and quality of life).[9] However, diagnostic studies are meant to supplement, not replace, a comprehensive patient history and physical examination. Table 16 summarizes examples of diagnostic studies used in patients with pain.

Table 12. Preoperative Assessment and Patient Education Recommendations

- Establish a positive relationship with patients and/or families.
- Obtain a pain history.
- Educate the patient about pain assessment (e.g., methods, frequency) and pharmacologic and nonpharmacologic management strategies.
- Explore concerns/dispel misconceptions about use of pain medications, side effects, and addiction.
- Develop a strategy for postoperative analgesia in collaboration with the patient based on type of surgery, expected severity of postoperative pain, underlying medical conditions, the risk-benefit ratio and costs of available techniques, and patient's preferences and/or previous experience(s) with pain.
- Involve the patient in selecting an appropriate[a] pain measurement tool (e.g., NRS, VAS), and review its features with the patient.
- Educate the patient (and/or families) about their responsibilities in pain management (e.g., providing a factual report of pain, preventing or halting pain before it has become well established). Negotiate a criterion (e.g., a score of 3-4 on a 10-point pain intensity scale) that will result in a dose increment or other intervention.
- Document the patient's preferred pain assessment tool and the goals for pain control (pain score).

Sources: References 5 and 17.

[a]Factors that help to determine the appropriate tool include: 1) the patient's age; physical, emotional, or cognitive status; and preference; 2) the assessor's expertise, time, and degree of effort available; and 3) the institution's requirements for monitoring and documentation for quality assurance purposes.

NRS: numeric rating scale; VAS: visual analog scale.

Table 13. Postoperative Assessment and Patient Education Recommendations

- Assess multiple indicators of pain, including 1) patient perceptions (self-report), 2) cognitive attempts to manage pain, 3) behavioral responses (e.g., splinting the operative site, distorted posture, decreased mobility, insomnia, anxiety, depression), and 4) physiological responses (vital signs).
- Accept the patient self-report, and only substitute behavior and/or physiological responses if the patient is unable to communicate.
- Measure pain at rest and during activity (e.g., moving, deep breathing, coughing).
- Assess pain frequently during the immediate postoperative period: 1) at regular intervals, consistent with surgery type and pain severity (e.g., every 2 hours while awake for 1 day after surgery); 2) with each new report of pain; and 3) at a suitable interval after each analgesic intervention (e.g., 30 minutes after parenteral drug therapy, and 1 hour after oral analgesics). Increase the frequency of assessment for changing interventions or inadequate pain control.
- Record pain intensity and response to any interventions (including side effects) in a visible and accessible place (e.g., bedside chart).
- Immediately evaluate instances of unexpected intense pain, particularly if sudden or associated with evidence of potential complications.[a]
- Consider all reasons for any discrepancies between a patient's self-report of pain and his or her behavior. Such discrepancies may reflect good coping skills or diversionary activities (e.g., distraction, relaxation techniques). Alternatively, a patient may be denying pain because of stoicism or fear of inadequate pain control.
- Give special consideration to needs of special populations, and be aware of potential barriers to effective communication (e.g., mental, cognitive, or hearing impairments; language barriers; cultural traditions).
- Revise the management plan, as needed, if pain behavior is observed or the patient expresses feelings of inadequate pain control.
- Prior to patient discharge, review with the patient the interventions used and their efficacy; provide specific discharge instructions regarding outpatient pain management.

Sources: References 5 and 17.

[a]Signs such as fever, hypertension, tachycardia, or oliguria may be indicative of complications including wound dehiscence, infection, or deep venous thrombosis.

B. Measurement of Pain: Common Assessment Tools

Tools for pain assessment include unidimensional scales and multidimensional tools. The former (i.e., rating scales) usually assess a single dimension of pain, patient self-report of pain intensity. Although useful for assessing acute pain of clear etiology (e.g., postoperative pain), rating scales may oversimplify the assessment of some types of pain.[12] Therefore, experts recommend the use of multidimensional tools in the assessment of complex or persistent pain.

1. Unidimensional Scales

Rating scales provide a simple means for patients to rate pain intensity. Typical scales use numeric (e.g., 0-10), verbal (word), or visual (image) descriptors to quantify pain or pain relief. The tool should be appropriate for the patient's developmental, physical, emotional, and cognitive status, as well as reliable, valid, and easy to use.[5] Examples of these scales include the following (see Table 17):

- *Numeric rating scale (NRS):* The NRS is the most commonly used rating scale. Patients rate their pain on a 0-to-10 scale or a 0-to-5 scale, with 0 representing "no pain at all" and 5 or 10 representing "the worst imaginable pain." Pain intensity levels are measured at the initial encounter, following treatment, and periodically, as suggested by guidelines and the clinical situation.
- *Visual analog scale (VAS):* The VAS consists of a 10-cm line, with anchors at either end. One end is marked "no pain" and the other end is marked

Table 14. Additional Aspects of the Patient History in Patients With Chronic Noncancer Pain

- Pain treatment history: full review of results from past work-ups and treatments as well as patient's utilization of health care resources (e.g., office visits).
- Comprehensive psychosocial evaluation focused on: 1) patient responses to chronic pain (e.g., coping skills, avoidance of stressors, presence of chronic pain syndrome); 2) what the pain means to the patient; 3) evidence of family, legal, or vocational issues; and 4) expectations of family members, employers, attorneys, or social agencies (e.g., Social Security Administration). This evaluation may involve interviewing family members, too.
- Psychiatric interview to: 1) identify any psychological symptoms (e.g., depression, anxiety, anger), coexisting psychiatric disorders, or psychological traits; 2) evaluate suicide risk in patients with clinical signs of depression (e.g., sleep or appetite disturbances, hopelessness); and 3) identify history of events (e.g., severe or extreme trauma) that may lead to somatization or pain.
- Psychometric tests,[a] when appropriate, to provide information about the pain, associated problems, and any coexisting psychopathology.
- Assessment of function and any disability to determine the patient's ability to perform daily activities (e.g., household chores, work tasks, leisure interests) and function autonomously, as well as the presence and levels of disability. Questionnaires such as the Pain Disability Index can be used to assess levels of disability, when appropriate. More formal evaluation of disability may be needed in some cases (e.g., application for disability benefits).
- Review of results with patient and family: This is the first step in the treatment of chronic noncancer pain, providing an opportunity to establish the rehabilitative focus of pain management and set realistic treatment goals.

Sources: References 8 and 18.

[a]Psychometric tests include pain-related instruments (e.g., McGill Questionnaire, Multidimensional Pain Inventory, Beck Depression Inventory) and personality assessment instruments (e.g., Minnesota Multiphasic Personality Inventory-2, Coping Strategies Questionnaire).

"pain as bad as it could be" or "the worst imaginable pain." The patient marks the place on the line to indicate his or her pain intensity. The clinician then measures the line with a ruler and assigns a score.[28]

- *Categorical scales:* Categorical scales provide a simple means for patients to rate pain intensity using verbal or visual descriptors of the pain. Melzack and Torgerson[29] introduced a scale with five verbal descriptors (i.e., mild, discomforting, distressing, horrible, and excruciating). The Faces Pain Scale (FPS) for Adults and Children[16] and the Wong-Baker Faces Rating Scale (for children)[30-31] are categorical scales with visual descriptors. The FPS consists of eight images of faces with various expressions (e.g., smiling, frowning, grimacing). The patient selects the face that is consistent with his or her current level of pain.

2. Multidimensional Tools

Although not used as often as they should be, multidimensional tools provide important information about the pain's characteristics and effects on the patient's daily life.[12,22] These tools are designed for patient self-report, but a clinician may assist the patient. Examples of multidimensional tools include (see Table 18):

- *Initial Pain Assessment Tool*: This tool, which was developed for use in the initial patient evaluation, elicits information about characteristics of the pain, the patient's manner of expressing pain, and the effects of the pain on the patient's life (e.g., daily activities, sleep, appetite, relationships, emotions).[7] It includes a diagram for indicating pain location(s), a scale for the patient to rate pain intensity, and a space for documenting additional comments and management plans.
- *Brief Pain Inventory (BPI):* This tool is quick and easy to use and quantifies both pain intensity and associated disability.[12,34-35] It consists of a series of questions that address aspects of the pain experienced over the preceding 24 hours (e.g., pain location and intensity, impact on the patient's life, type and effectiveness of any treatments). The BPI generally takes about 5 to15 minutes to complete and is useful for a variety of patient populations.[36-37]
- *McGill Pain Questionnaire (MPQ):* The MPQ is one of the most extensively tested multidimensional scales in use.[32] This tool assesses pain in three dimensions (i.e., sensory, affective, and evaluative) based on words that patients select to describe their pain. The MPQ can be combined with other tools to improve diagnostic accuracy.[12] A briefer form of the MPQ, the short-form McGill Pain Questionnaire, is also available.[39]

A number of other multidimensional tools for pain assessment exist.[12] Some are designed to measure chronic pain in general, while others are specific to particular pain syndromes. In addition, some quality of life instruments (e.g., Medical Outcome Study Short-Form 36 Health Survey Instrument) assess pain.

Table 15. Physical Examination of a Patient With Pain

Region	Rationale, Methods, and Potential findings
General	Observe and/or identify: • Patient's general appearance and vital signs • Evidence of overt abnormalities (e.g., weight loss, muscle atrophy, deformities, trophic changes) • Any subjective manifestations of pain (e.g., grimacing, splinting)
Site of pain	Inspect the pain site(s) for abnormal appearance or color of overlying skin or visible muscle spasm Palpate the site(s) to assess for tenderness and correlate tenderness with any associated subjective or objective findings Use percussion (or jarring) to elicit, reproduce, or evaluate the pain and any tenderness on palpation Use the brush, pinch, pin prick, and/or scratch tests to assess for allodynia, hyperalgesia, or hyperesthesia Determine the effects of physical factors (e.g., motion, applied heat or cold, deep breathing, changes in position) on pain
Other regions	Examine other regions as directed by the patient history or assessment of pain site
Neurological system	At minimum, perform a screening neurological examination (i.e., assess cranial nerves, spinal nerves, sympathetic nervous system function, coordination, and mental status) to screen for: • Sensory deficits (e.g., impaired vision or hearing) or abnormal sensations (e.g., paresthesia, dysesthesia, allodynia, hyperpathia) • Motor abnormalities or deficits (e.g., weakness, exaggerated or diminished reflexes) • Lack of coordination • Evidence of sympathetic nervous system dysfunction (e.g., skin flushing, unusual sweating) • Abnormalities or deficits in orientation, recent or remote memory, parietal sensory function, language function, and mood
Musculoskeletal system	Observe and/or identify: • Body type, posture, and overall symmetry • Abnormal spine curvature or limb alignment and other deformities • Abnormal movements and/or irregular gait during walking • Range of motion (spine, extremities) For muscles in neck, upper extremities, trunk, and lower extremities: • Assess multiple parameters (e.g., tone, volume, contour, strength and power, range of motion) • Observe for any abnormalities (e.g., weakness, atrophy, hypertrophy, irritability, tenderness, trigger points)

Source: Reference 8.

Table 16. Examples of Diagnostic Tests

Type	Definition	Potential Uses
Screening laboratory tests	Includes CBC, chemistry profile (e.g., electrolytes, liver enzymes, BUN, creatinine), urinalysis, ESR	Screen for illnesses, organ dysfunction
Disease-specific laboratory tests	Includes autoantibodies, sickle cell test	Autoimmune disorders, SCD
Imaging studies	Includes radiographs (x-rays), CT, MRI, US, myelography	Detection of tumors, other structural abnormalities
Diagnostic procedures	Includes lumbar puncture, thoracentesis, paracentesis, biopsy	Detection of various illnesses
Electrodiagnostic tests • EMG • NCS	Include EMG (direct examination of skeletal muscle via needle electrodes) and NCS (examination of conduction along peripheral sensory and motor nerves or plexuses)	Detection of myopathies, some neuropathies, MS
Diagnostic nerve block	Nerve block (injection of a local anesthetic to determine the source/mechanism of the pain)	Multiple uses,[a] including: • Identification of structures responsible for the pain (e.g., sacroiliac or facet joint blocks) • Differentiation between types of pain

Sources: References 19-20a.

[a]Diagnostic neural blockade (pain blocks) with a local anesthetic may be useful in determining the anatomic source of the pain, nociceptive pathways, or the contribution of the sympathetic nervous system to the pain.[20a] They also may allow differentiation between local vs. referred pain, somatic vs. visceral pain, or central vs. peripheral pain.

BUN: blood urea nitrogen; CBC: complete blood count; CT: computed tomography; EMG: electromyography; ESR: erythrocyte sedimentation rate; MRI: magnetic resonance imaging; MS: multiple sclerosis; NCS: nerve conduction studies; SCD: sickle cell disease; US: ultrasound.

Table 17. Unidimensional Pain Assessment Tools

Scale	Administration	Advantages	Disadvantages	Comments
Numeric rating scale (NRS)	Verbal or visual	Easy to use Simple to describe High rate of adherence Flexible administration (including by telephone) Validated for numerous settings and pain types (acute, cancer, CNCP)	Less reliable for some patients (very young or old; patients with visual, hearing, or cognitive impairment)	Most commonly used rating scale
Visual analog scale (VAS)	Visual	Efficient to administer Valid in patients with chronic pain, older than age 5 years, rheumatic disease	Time-consuming scoring Controversial validity Can cause patient confusion Poor reproducibility with cognitive dysfunction	FPS generally preferred to the VAS for assessment in the elderly
Faces pain scale (FPS)	Visual	Perceived as easier than NRS or VAS No influence of culture, gender, or ethnicity Useful in individuals with difficulty communicating (e.g., children, elderly, individuals with limited language fluency or education)	Potential for distorted assessment (i.e., patients' tendency to point to the center of such scales) Need for instrumentation (i.e., a printed form)	Good alternative for patients with difficulty communicating

Sources: Reference 7, 11-13, 16, and 21-27.
CNCP: chronic noncancer pain; FPS: Faces Pain Scale; NRS: numeric rating scale; VAS: visual analog scale.

Table 18. Multidimensional Pain Assessment Tools

Scale	Administration	Advantages	Disadvantages or Comments
Brief Pain Inventory (BPI)	Visual	Reliable and valid for many clinical situations (e.g., cancer pain, arthritis pain, pain associated with HIV infection) and across cultures and languages Available in multiple languages Quick, quantifies pain intensity and disability	Used both clinically and in research Good choice of measure in patients with progressive conditions
Initial Pain Assessment Inventory (IPAI)	Visual	May be completed by patient or clinician Includes diagram for illustrating sites of pain	
McGill Pain Questionnaire (MPQ)	Verbal	Extensively tested Assesses sensory and affective dimensions of pain Short form takes only 2-3 minutes	Long form takes 5-15 minutes to complete Some patients confused by vocabulary Total score, but not individual scale scores, is considered valid measure of pain severity
Memorial Pain Assessment Card	Visual	Rapid to use Correlated with other longer measures of pain and mood Can fold card so that the patient views only one scale at a time	Assesses pain relief and mood on VAS and adds a set of adjectives reflecting pain intensity
Pain drawing	Written	May demonstrate nature of pain at a glance (e.g., radiculopathy, peripheral neuropathy, trigeminal neuralgia, arthritis) Helps to avoid overlooking pain that the patient fails to mention	

Sources: References 7, 12, and 32-38.
BPI: Brief Pain Inventory; HIV: human immunodeficiency virus; IPAI: Initial Pain Assessment Inventory; MPQ: McGill Pain Questionnaire; VAS: Visual analog scale.

3. Neuropathic Pain Scale

Although the Short Form MPQ[39] provides some information about neuropathic pain, it does not quantify it. The recently developed Neuropathic Pain Scale provides information about the type and degree of sensations experienced by patients with neuropathic pain.[27] It evaluates eight common qualities of neuropathic pain (i.e., sharp, dull, hot, cold, sensitive, itchy, and deep versus surface pain). The patient rates each item on a scale from 0 to 10, with 0 for none and 10 for the "most imaginable." Although still in its developmental form, this scale may hold diagnostic and therapeutic promise.[7] Early data suggest that this scale is easy to use and sensitive to treatment effects.[27]

C. Reassessment of Pain

Reassessment of pain is integral to effective pain management. Many factors influence its frequency, scope, and methods. This section reviews some approaches to reassessment in common clinical settings and situations.

1. Frequency

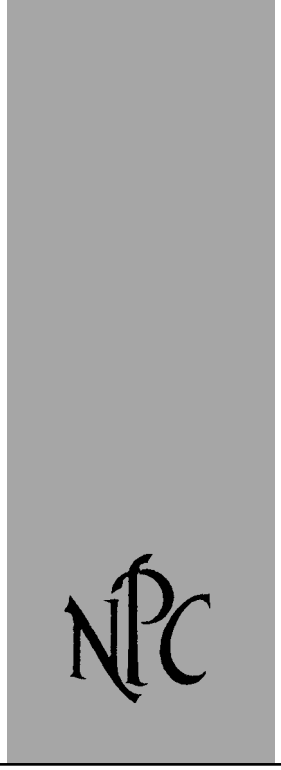
The 1992 Agency for Health Care Policy and Research[b] CPG states that pain should be reassessed: 1) within 30 minutes of parenteral drug administration, 2) within one hour of oral drug administration, and 3) with each report of new or changed pain.[5] However, these recommendations pertain to the reassessment of acute pain in an acute care setting. Multiple factors determine the appropriate frequency of pain reassessment, including characteristics of the pain (e.g., duration, severity), patient factors and needs, the clinical setting, and pain management plan (i.e., type of drug or intervention).

Reassessing pain with each evaluation of the vital signs (i.e., as a fifth vital sign) is useful in some clinical settings. However, the frequency of vital signs checks in others settings suggests the need for more or less frequent reassessment. Clinicians should instruct outpatients to contact them to report changes in the pain's characteristics, side effects of treatment, and treatment outcomes. Periodic reassessment is recommended in patients with chronic pain to evaluate improvement, deterioration, or treatment-related complications.[9,40] Residents of long-term health care facilities should be assessed for pain upon admission, at quarterly reviews, with changes in the patient's medical condition, and whenever pain is suspected.[41]

2. Scope and Methods

The scope and methods of reassessment vary with factors including the setting, characteristics of the pain, the patient's needs and medical condition, and responses to treatment. Routine screening for pain with a pain rating scale provides a useful means of detecting unidentified or unrelieved pain. Appropriate tools, as well as terms synonymous with pain (e.g., burning, discomfort, aching, soreness, heaviness, tightness), should be used to screen elderly patients.[40] The presence of any pain indicates the need for further assessment, consideration of pain-relieving interventions, and post-intervention follow-up.[3] For example, reassessment of pain in a stable and comfortable postoperative patient may be relatively simple and brief (i.e., score on NRS alone). However, sudden, unexpected intense pain, especially if associated with altered vital signs, should prompt immediate and thorough assessment for potential complications (e.g., wound dehiscence, infection, or deep venous thrombosis).[5] Patients who have not responded to treatment and/or have complex types of pain (e.g., chronic pain, neuropathic pain) often require more comprehensive reassessment of pain. A pain diary may facilitate this process.[9] A pain diary or log is a patient-generated record that is used to track various aspects of the pain and its management (e.g., pain intensity, associated activities, medication use, side effects, and other responses to treatment).

[b]The Agency for Health Care Policy and Research is now the Agency for Health Care Research and Quality.



Section III:

Types of Treatments

A. Pharmacologic Treatment

Treatments for pain can be broadly categorized as pharmacologic and nonpharmacologic. This section of the monograph provides an overview of: 1) a commonly used analgesic classification system, 2) some commonly used analgesic classes and individual drugs, and 3) general principles of pharmacologic treatment.

1. Drug Classifications and Terminology

Pharmacologic treatment is the mainstay of pain therapy. Almost half of individuals who suffer from pain choose a nonprescription analgesic as their initial choice for pain relief.[1] Up to one in five Americans take an over-the-counter or prescription analgesic on a daily basis.[2] As with types of pain, multiple systems for classifying analgesics exist. In the below system, analgesics are broadly categorized as:

- *Nonopioid analgesics (nonopioids)*: acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and other salicylic acid derivatives
- *Opioid analgesics (opioids)*: mu opioid agonists (i.e., morphine-like agonists) and agonist-antagonist opioids
- *Adjuvant analgesics or co-analgesics:* a diverse group of drugs, with primary indications for conditions other than pain, with analgesic properties relevant to some conditions. Commonly used adjuvant analgesics include antiepileptic drugs (AEDs), tricyclic antidepressants (TCAs), and local anesthetics (LAs).

Variations of this classification system exist,[a] and terminology in the field is also evolving. The term "opioids" has replaced "narcotics," and "co-analgesics" is an alternate term for "adjuvant analgesics."

[a] Because acetaminophen has some, albeit extremely limited, anti-inflammatory properties,[3] some experts consider acetaminophen an NSAID and use the term "NSAIDs" rather than "nonopioids." Other experts disagree with this classification due to the different mechanisms of action and side effects of these drugs.

2. Common Analgesic Agents

a. Nonopioids

i. Mechanism of action and effects

The primary mechanism of action of NSAIDs is inhibition of the enzyme cyclooxygenase (COX) which blocks prostaglandin synthesis.[4,5] Acetaminophen, another nonopioid, appears to act mostly via a central mechanism.[3,6-7] All nonopioids have anti-inflammatory, antipyretic, and analgesic effects, but the anti-inflammatory effect of acetaminophen is essentially negligible.[8] The analgesic effect of NSAIDs is prompt (minutes to hours), whereas the anti-inflammatory effect may take longer (1-2 weeks or longer).[9] This latter effect can indirectly relieve some pain by reducing tissue swelling.

The relatively recent discovery that COX has two isoforms, COX-1 and COX-2, has advanced NSAID pharmacology. COX-1 is constitutively expressed in most normal tissues,[10] but plays an especially important role in the gastrointestinal (GI) tract, kidneys, and platelets; COX-1 primarily produces prostaglandins with beneficial effects (e.g., regulation of blood flow to the gastric mucosa and kidneys).[8,11] In contrast, COX-2 is normally not present but may be induced in response to inflammatory stimuli; COX-2 primarily produces prostaglandins that activate and sensitize nociceptors (see I.B).[b] Nonselective NSAIDs inhibit COX-1 and COX-2, which contributes to both their therapeutic actions and side effects. The recently introduced COX-2 selective inhibitors (or "coxibs") selectively inhibit COX-2 without affecting COX-1 at therapeutic doses.[15,16] Thus, coxibs offer the advantage of efficacy comparable to that of nonselective NSAIDs, with a reduced risk of certain side effects.[17-18] The coxibs affect COX-2 both centrally and peripherally.

ii. Indications and uses

Nonopioids relieve a variety of types of acute and chronic pain (e.g., trauma, postoperative, cancer, arthritis pain) and are especially effective for certain types of somatic pain (e.g., muscle and joint pain, bone/dental pain, inflammatory pain, postoperative pain) (Table 19).[19-21] Acetaminophen and NSAIDs, alone, often relieve mild pain, and some NSAIDs relieve certain types of moderate pain (Table 19).[51] Even

[b] The division of function between COX-1 and COX-2 is not perfect. COX-1 produces some prostaglandins that contribute to inflammation.[12] COX-2 is constitutively expressed in some organs (e.g., the kidney) where it produces prostaglandins with protective effects.[13-14]

Table 19. Examples of Nonopioid Analgesics

Chemical Class	Generic Name	Indications	Usual Oral Dosing Interval or Frequency	Dosage Forms and Routes of Administration	Major Side Effects	Comments
Paraaminophenols	Acetamin-ophen	Mild to moderate pain due to multiple causes including head-ache, toothache, muscular aches, backache, menstrual cramps, arthritis, common cold, and flu; fever reduction	q 4-6 h[a]	Multiple oral (e.g., tablets, caplets, powder, elixir, suspensions, liquid); rectal suppositories	Acute overdose: hepatic necrosis (liver damage)[b] Chronic overdose: liver toxicity, nephrotoxicity, thrombocytopenia	Lacks anti-inflammatory effects of NSAIDs, but no adverse effects on gastric mucosa or platelets Analgesic and antipyretic effects comparable to aspirin Useful in patients intolerant of NSAIDs and for fever control in children with flu
Salicylates	Aspirin Diflunisal CMT	Mild to moderate pain due to multiple causes including headache, toothache, sinus pain, muscular aches, bursitis, backache, sprains, arthritis, pain due to fever, cold, flu	ASA: q 4-6 h[a] Diflunisal: q 8-12 h CMT: QD, BID, or TID	Multiple oral (caplet, tablet, gelcap, effervescent tablet, gum, liquid); rectal suppositories	NSAID class effects[c] Diflunisal hypersensitivity: life-threatening reaction that may involve multiple organs	Combination formulations available (aspirin and acetaminophen, and/or caffeine) Diflunisal causes less GI irritation and antiplatelet effects than aspirin
Propionic acid derivatives	Ibuprofen	Mild to moderate pain, including pain associated with the common cold, headache, toothache, muscular aches, backache, menstrual cramps, and arthritis; fever reduction	q 4-6 h	Oral (tablets, caplets, geltabs, suspension); rectal suppositories	NSAID class effects Toxic amblyopia	Commonly used NSAID OTC formulations available Combinations with codeine and hydrocodone available Fewer GI effects than other non-selective NSAIDs
	Naproxen	RA, OA, AS, JA, tendonitis, bursitis, gout, primary dysmenorrhea	q 6-12 h	Tablets, oral suspension, delayed-release tablets	NSAID class effects Other: pseudoporphyria	OTC formulations available Delayed-release tablets are NR for initial treatment of acute pain
	Ketoprofen	Signs and symptoms of OA and RA, pain, and primary dysmenorrhea	q 6-8 h; q 24 h for ER form	Capsules, ER capsules	NSAID class effects	OTC formulations available ER capsules NR for treatment of acute pain
	Flurbiprofen	OA, RA	BID, TID, or QID	Tablets	NSAID class effects	
	Oxaprozin	Acute and long-term management of OA and RA	q 24 h	Caplets	NSAID class effects Other: photosensitivity, rash	Long half-life (55 hours), thus can be given once daily
Indoleacetic acids	Indomethacin	Moderate to severe OA, RA, AS; acute gouty arthritis; acute painful shoulder (bursitis and/or tendonitis)	BID, TID, or QID	Oral (capsules, suspension, slow-release capsules) rectal suppositories	NSAID class effects Ocular effects (corneal deposits, retinal disturbances) Exacerbation of Parkinson's disease, epilepsy, or psychiatric disorders	Limited use due to side effects
Benzothiazine derivatives (oxicams)	Piroxicam	Acute and long-term management of OA and RA	q 24 h	Capsules	NSAID class effects Insomnia	Single daily dose
	Meloxicam	OA	q 24 h	Tablets	NSAID class effects	Single daily dose

Table 19. Examples of Nonopioid Analgesics (continued)

Chemical Class	Generic Name	Indications	Usual Oral Dosing Interval or Frequency	Dosage Forms and Routes of Administration	Major Side Effects	Comments
Pyrroleacetic acid derivatives	Diclofenac	OA, RA, AS, primary dysmenorrhea	BID, TID, or QID ER form q 24 h	Tablets, ER tablets	NSAID class effects Other: acute hemolytic anemia, aseptic meningitis, rash Avoid use in patients with porphyria Combination with misoprostol contraindicated in pregnant women	Lower risk of GI effects
	Ketorolac	Short term (<5 days) treatment of moderately severe acute pain that requires analgesia at the opioid level (e.g., postoperative pain)	Varies for parenteral therapy q 4-6 h oral form	Oral (tablets), IV (injector, sterile cartridges)	NSAID class effects Warning indicating potential for serious NSAID side effects if used inappropriately NR for minor or chronic pain	Parenteral form useful when PO NSAIDs are undesirable and for opioid-sparing effect Combined oral and parenteral therapy should not exceed 5 days IV administration provides pain relief comparable to 10 mg of IM morphine
Selective COX-2 inhibitors[d]	Rofecoxib	OA, acute pain in adults, primary dysmenorrhea	q 24 h	Tablets, oral suspension	Most common: URI, nausea, HTN NSAID class effects less likely (see Comments) Rare aphylactoid reactions	PI labeling lists some of the same adverse reactions as non-selective NSAIDs, but sparing of COX-1-mediated prostaglandins reduces the risk of serious GI side effects and renal toxicity Also does not alter platelet aggregation nor alter effects of low-dose aspirin on platelets
	Celecoxib	OA, RA, FAP	q 12 or 24 h	Capsules	Most common: HA, URI, dyspepsia NSAID class effects less likely (see Comments) Rare anaphylactoid reactions	PI labeling lists some of the same adverse reactions as non-selective NSAIDs, but sparing of COX-1 mediated prostaglandins reduces the risk of serious GI side effects and renal toxicity Also, no effects on platelet aggregation

Sources: References 8, 19-22, and 27-50.

[a]Some sources (e.g., 2001 Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements,[22] the American Pain Society's Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain,[19] McCaffery and Pasero[23]) list the dosing interval for aspirin and acetaminophen as 4 to 6 hours. Other sources (e.g., Agency for Health Care Policy and Research Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1)[24] list the dosing interval for these drugs as 4 hours.

[b]Use with caution in certain populations (i.e., patients with chronic alcoholism, liver disease, malnourishment).[19,25-26]

[c]Adverse effects of nonselective NSAIDs as a class include gastrointestinal problems (e.g., dyspepsia, ulcers, perforation, bleeding), liver dysfunction, bleeding due to inhibited platelet aggregation (i.e., "antiplatelet effect"), kidney problems (e.g., renal insufficiency, acute renal failure), hypersensitivity reactions (i.e., aspirin sensitivity), and CNS effects (e.g., attention and memory deficits, headache, dizziness, drowsiness).[19] Recommended monitoring includes standard laboratory tests (e.g., complete blood count, liver and kidney function) and stool guaiac test (for occult blood). NSAIDs are generally contraindicated in patients with a history of asthma, urticaria, or allergic-type reactions after taking NSAIDs, including aspirin.

[d]These agents selectively inhibit COX-2 activity and do not affect COX-1 activity at therapeutic doses.

AS: ankylosing spondylitis; ASA: aspirin; BID: twice daily; CMT: choline magnesium trisalicylate; CNS: central nervous system; COX-cyclooxygenase; ER: extended release; ESRD: end-stage renal disease; FAP: familial adenomatous polyposis; GI: gastrointestinal; HA: headache; HTN: hypertension; IM: intramuscular; IV: intravenous; JA: juvenile arthritis, NR: not recommended; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; OTC: over-the-counter; PI: package insert; PO: per os (by mouth); QD: once per day; QID: four times daily; RA: rheumatoid arthritis; TID: three times daily; URI: upper respiratory infection.

for moderate or severe pain that does require an opioid, nonopioids are often added to the regimen for their opioid-sparing effect (i.e., they lower the dose of opioid required).[19] Since nonopioids and opioids relieve pain via different mechanisms, combination therapy offers the potential for improved relief with fewer side effects. Nonopioids do not produce tolerance, physical dependence, or addiction.[19] Choice of NSAID is influenced by factors including medication tolerance, dosing frequency, and cost.[52]

iii. Routes of administration, formulations, and dosing

Patients usually take nonopioids orally, but other forms (e.g., rectal, topical, parenteral) of some drugs exist.[19] Numerous formulations of acetaminophen and aspirin, as well as some nonselective NSAIDs, are available without a prescription. In addition, some nonopioids are marketed in combination with other drugs (e.g., other nonopioids, opioids, caffeine, sedatives).

Onset and duration of analgesia and, therefore, dosing frequency reflect drug half-life and special formulations (e.g., sustained-release preparations). Some NSAIDs only need to be taken once a day. In contrast to most opioids, all nonopioids have a dosage ceiling.[19] This means that a dose is reached beyond which additional side effects, but not pain relief, can occur. Patient responsiveness to NSAIDs varies greatly, so a patient who has not responded to the maximum therapeutic dose of one NSAID should try another.[19]

iv. Side effects

Inhibition of COX-1 causes some of the side effects of nonselective NSAIDs. Adverse effects of nonselective NSAIDs as a class include GI problems (e.g., dyspepsia, ulcers, perforation, bleeding, liver dysfunction), bleeding (i.e., "antiplatelet effect"), kidney dysfunction, hypersensitivity reactions, and CNS effects.[19] Table 20 summarizes precautions and methods of managing these adverse events.

Despite these shared effects, the side effect profiles of individual drugs do differ (see Table 19). For example, some nonselective NSAIDs (e.g., ibuprofen, naproxen) are less likely than others (e.g., ketoprofen) to cause GI problems. Side effects are generally less likely to occur when drugs are used at low doses or for short periods in appropriately selected patients.[19] In addition, the risk of some side effects can be reduced by protective mechanisms (e.g., coadministration of misoprostol to reduce the risk of gastric ulcer).[19] Therefore, in some clinical circumstances, treatment with a nonselective NSAID is relatively safe and use of a selective COX-2 inhibitor is not necessarily warranted. Conversely, use of a selective COX-2 inhibitor may be preferable in some situations (e.g., preoperative period, bleeding disorder).

Acetaminophen or a selective COX-2 inhibitor may be an appropriate treatment alternative to nonselective NSAIDs in some patients. Acetaminophen does not damage the gastric mucosa or inhibit platelet aggregation and provides pain relief comparable to that of aspirin.[19] However, acetaminophen has negligible anti-inflammatory activity. In addition, acute or chronic overdose with acetaminophen may cause liver or kidney toxicity, so acetaminophen should be used with caution in patients with certain conditions (e.g., malnutrition, chronic alcoholism, liver disease).[25] Accidental overdosage also may occur in patients taking over-the-counter combination pain relievers containing acetaminophen.

Although product labeling for selective COX-2 inhibitors and nonselective NSAIDs is similar, evidence suggest that coxibs are less likely to cause certain side effects. For example, clinical trial data suggest that celecoxib produces comparable relief of rheumatoid arthritis (RA) pain and inflammation to diclofenac[57] and naproxen,[58] but a lower incidence of endoscopically diagnosed gastroduodenal ulcers. Celecoxib also appears to provide equal symptomatic relief of osteoarthritis (OA) pain to diclofenac but with fewer GI side effects.[59] Other data suggest that, due to its COX-1-sparing effect, celecoxib does not affect platelet function.[60]

Rofecoxib, another selective COX-2 inhibitor, is associated with similar advantages. In clinical trials, it provided comparable relief of OA pain to diclofenac and ibuprofen[61-62] and comparable relief of RA pain to naproxen.[18] In a comparison trial, rofecoxib therapy was associated with a lower 12-month cumulative incidence of GI tract perforations, symptomatic gastroduodenal ulcers, and upper GI tract bleeds (but similar incidence of dyspeptic GI side effects) than nonselective NSAIDs including ibuprofen, diclofenac, and nabumetone.[63] In a recent controlled study, rofecoxib did not alter platelet aggregation when administered alone nor alter the (desirable) anti-platelet effects of low-dose aspirin when used in combination therapy.[64] Thus, selective COX-2 inhibitors appear to have less severe GI side effects and do not affect platelet function.

Table 20. Class Effects of Nonselective NSAIDs

System	Side Effect	Precautions and Contraindications	Prevention and Management
GI	Dyspepsia, ulcer formation, perforation, bleeding (due to inhibited synthesis of PGs that regulate blood flow to gastric mucosa)	Patients at increased risk: • Elderly • History of GI disease (e.g., ulcer) • Concomitant steroid or anticoagulant therapy • High-dose NSAID therapy	Initiate treatment at low doses Take NSAID with food Avoid alcohol Co-administer gastroprotective agents (e.g., misoprostol, sucralfate, histamine$_2$-blockers)[a] Use NSAIDs with less risk of GI problems (e.g., ibuprofen, selective COX-2 inhibitors) Monitor patient with stool guaiac test (for occult blood) and complete blood count
GI	Liver dysfunction Rare hepatic necrosis	Patients at increased risk: • Alcoholics • History of liver disease Relative contraindications: • Elevated liver enzymes • Preexisting liver disease	Baseline and periodic monitoring of liver function enzymes
Heme	Bleeding due to: • Inhibited platelet aggregation[b] or "anti-platelet effect" (due to inhibition of PG synthetase) • Prolonged prothrombin time (due to drug interaction with oral anticoagulant)	Relative contraindications: • Anticoagulation • Coagulopathy • Thrombocytopenia Other patients at increased risk: • Surgical patients • Some patients with cancer	Use NSAIDs with minimal or no bleeding risk in high-risk patients (e.g., choline magnesium trisalicylate, selective COX-2 inhibitors) Consider replacing NSAID with acetaminophen Stop ASA therapy 1 week prior to surgery and most other NSAIDs 2-3 days prior to surgery
Renal	Renal insufficiency (uncommon) or acute renal failure (rare) Multiple causes, including inhibited synthesis of vasodilator PGs that preserve blood flow to kidneys	Patients at highest risk for renal insufficiency or failure: • Elderly • Volume-depleted • Preexisting renal disease • Coexisting illness (e.g., HTN, CHF, diabetes, cirrhosis, multiple myeloma) • Taking diuretics or medications that limit renal blood flow	Usually resolves with drug discontinuation For high-risk patients: • Use low doses • Monitor kidney function • Avoid indomethacin
Immune	Hypersensitivity reactions: • Respiratory reaction • Urticaria-angioedema reaction	Patients who are sensitive to aspirin may be cross-sensitive to other NSAIDs	Monitor patients for asthma, rhinitis, and nasal polyps (respiratory reaction) or wheals, urticaria, hypotension, shock (urticaria-angioedema reaction) Seek appropriate emergency treatment, as needed
CNS	CNS dysfunction including attention or memory deficits, headache, tinnitus	Patients at increased risk: • Elderly • Concomitant use of medications affecting CNS function	To manage cognitive dysfunction: • Lower dose • If dysfunction persists, discontinue NSAID • Switch to another NSAID and drug class

Sources: References 9, 19, 21, and 53-56.

[a]Consider gastroprotective agents, particularly in elderly patients and patients with a history of peptic ulcer disease, GI bleeding, or cardiovascular disease.[9]

[b]Aspirin causes irreversible inhibition of platelet aggregation, and other nonselective NSAIDs cause reversible inhibition of platelet aggregation.[19]

ASA: aspirin; CHF: congestive heart failure; CNS: central nervous system; COX: cyclooxygenase; GI: gastrointestinal; HTN: hypertension; NSAID: nonsteroidal anti-inflammatory drug; Heme: hematologic; PGs: prostaglandins.

b. Opioids

i. Mechanism of action and effects

Opioids bind to opioid receptors in the central nervous system (CNS) to: 1) inhibit the transmission of nociceptive input from the periphery to the spinal cord, 2) activate descending inhibitory pathways that modulate transmission in the spinal cord, and 3) alter limbic system activity (see I.B).[65-68] Thus, opioids modify sensory and affective aspects of pain. The different actions of opioids (i.e., agonist and antagonist) at various opioid receptors (e.g., mu, kappa, and delta) provide one means of classification. In this system, opioids are broadly classified as mu agonists or agonist-antagonists. Because experts do not recommend use of agonist-antagonists as first-line analgesics,[19,24] this discussion focuses

on mu agonists.

ii. Indications and uses

Opioids are used to treat moderate to severe pain that does not respond to nonopioids alone.[19] They are often combined with nonopioids because this permits use of lower doses of the opioid (i.e., dose-sparing effect). Nearly all types of pain respond to opioids; however, nociceptive pain is generally more responsive to opioids than neuropathic pain,[69] which may require higher doses of opioids.[66,70] Opioids play a major role in the treatment of acute pain (e.g., trauma, postoperative pain), breakthrough pain, cancer pain, and some types of chronic noncancer pain (CNCP).[19,71] Because responsiveness to opioids varies greatly among individuals, a patient who has failed to respond to an adequate trial of one opioid should try another (Table 21).[19] Although opioids vary in potency, more potent agents are not necessarily superior. Opioids are also categorized as weak opioids and strong opioids (Table 21).

Routes of administration, formulations, and dosing

Opioids are administered via multiple routes (e.g., oral, sublingual, rectal, parenteral, transdermal, intrathecal, epidural). Oral or transdermal administration is generally preferred for chronic treatment.[19] Intramuscular (IM) administration, especially repeated, should not be used due to its multiple disadvantages (e.g., pain, unreliable absorption, tissue fibrosis).[19,24]

Short-acting drugs often are used to manage intermittent pain and breakthrough pain (i.e., pain that "breaks through" pain relief provided by ongoing analgesia).[20] Long-acting and sustained-release opioids are useful for patients with continuous pain, as they lessen the severity of end-of-dose pain and often allow the patient to sleep through the night.[19] Most opioids may be given around the clock (ATC) for continuous pain or on an as-needed basis (PRN). ATC dosing is recommended after an optimal dose is established by dose titration.[19] Dose titration involves administering a small starting dose and gradually increasing or decreasing the dose based on levels of pain relief and side effects.

In contrast to nonopioids, strong mu agonist opioids do not have a ceiling effect (i.e., a dose beyond which no additional analgesia is achieved).[69] However, many opioids are marketed in combination with a nonopioid, which may limit the maximum dose.[19] The accumulation of toxic metabolites of some opioids (e.g., meperidine) also limits dose increases as well as treatment duration.[69,96] If these events preclude adequate pain relief, another opioid should be substituted. Equianalgesic dosing charts help clinicians determine the appropriate starting dose of an opioid when changing routes of administration or when changing from one opioid drug to another (see Table 22). These charts list analgesic doses (oral and parenteral) that are approximately equivalent in ability to provide pain relief.

iv. Side effects

Binding of mu agonist opioids to receptors in various body regions (e.g., CNS, GI tract) results in therapeutic effects and side effects. Side effects of mu agonist opioids as a class include sedation, mental clouding or confusion, respiratory depression, nausea, vomiting, constipation, pruritus (itching), and urinary retention. With the exception of constipation, these side effects tend to subside with time. Tables 23 and 24, respectively, summarize general and specific approaches to side effect prevention and management.

Most opioids should be used with caution in patients with impaired ventilation, bronchial asthma, liver failure, or increased intracranial pressure.[19] Opioid-induced respiratory depression is usually short-lived, antagonized by pain, and most common in the opioid-naive patient.[97]

c. Antiepileptic drugs

i. Mechanism of action and effects

AEDs are a type of adjuvant analgesic. The increasing use of AEDs for neuropathic pain is based on their ability to reduce membrane excitability and suppress abnormal discharges in pathologically altered neurons.[98-100] However, the exact basis of their analgesic effects is unclear. It does not appear to be specifically related to their antiepileptic activity. Other drugs that suppress seizures (e.g., barbiturates) do not relieve pain, and AEDs with effective antiepileptic activity do not necessarily have good analgesic activity.[101]

ii. Indications and uses

AEDs (Table 25) are used to treat neuropathic pain, especially lancinating (i.e., episodic shooting, stabbing, or knife-like) pain from peripheral nerve syndromes.[19,102-103] Most of this use is "off-label." Exceptions include two first-generation AEDs, carbamazepine and valproate, which have FDA approval for the management of trigeminal neuralgia and migraine prophylaxis, respectively. Phenytoin was the first AED used to treat pain,

Table 21. Examples of Opioid Analgesics

Generic Name	Indications	Usual Dosing Interval	Routes of Administration[a] and Dosage Forms	Potential Side Effects[b]	Comments
Morphine	Severe acute pain (e.g., trauma, postoperative pain, MI), cancer pain, chronic pain	Varies with IR and CR	PO (IR and CR), PR, IV, SC, EA, IA, SL	Mu agonist class side effects[c] Class precautions, warnings, and contraindications[d] Metabolite can accumulate in setting of RF or hepatic dysfunction	Used as a standard of comparison for all opioid drugs; can stimulate histamine release IR and CR oral preparations available CR tablets are to be taken whole and must not be broken, chewed, or crushed, to prevent potential toxic dosage
Hydromorphone	Oral: management of pain where opioid therapy is appropriate Parenteral: moderate to severe pain (e.g., trauma, MI, surgery, burns, renal colic, biliary colic, cancer)	4-6 h for oral and parenteral 6-8 h for rectal	PO, PR, IV, SC, EA, IA	Mu agonist class side effects, precautions, warnings, and contraindications	Useful alternative to morphine Available as high-potency injectable that facilitates SC administration
Fentanyl	Severe acute pain, cancer pain, CNCP TD fentanyl is only indicated for treatment of chronic pain that requires continuous administration and cannot be managed by lesser means	Varies with ROA and form 72 h for TD fentanyl	IV, EA, IA, TD, OTFC	Mu agonist class side effects, precautions, warnings, and contraindications TD fentanyl is contraindicated for acute pain, postoperative pain, mild or intermittent pain responsive to PRN or nonopioid therapy, and at doses above 25 mcg/h at the initiation of opioid therapy TD fentanyl should not be used in children <12 years or patients <18 years who weigh <110 lb, except in research setting	TD and oral transmucosal formulations available, including OTFC (fentanyl in sweetened matrix) IV fentanyl is fast-acting and it is often combined with benzodiazepines for procedural analgesia and sedation TD fentanyl is long-acting and can control pain for up to 72 hours but a small number of patients may require q 48-hour dosing Ensure patients follow the correct patch application procedure for TD fentanyl and avoid direct exposure of application site to heat
Oxycodone	Moderate to moderately severe pain (e.g., trauma, postoperative pain, musculoskeletal disorders, abdominal pain, dental pain, cancer pain) CR formulation for moderate to severe pain where opioid is required for an extended period of time	Varies with IR and CR	PO (IR and CR)	Mu agonist class side effects, precautions, warnings, and contraindications CR tablets are to be taken whole and must not be broken, chewed, or crushed, to prevent potential toxic dosage CR (80 and 160 mg) tablets for use in opioid-tolerant patients only	IR and CR preparations Available as single entity and in combination with a nonopioid Can be used like oral morphine for severe pain Often combined with a nonopioid for moderate pain
Meperidine	Moderate to severe pain (e.g., migraine, trauma, postoperative pain, acute abdominal pain)	3-4 h[e]	PO, IV SC, EA, IA	Mu agonist class side effects, precautions, warnings, and contraindications High doses may cause agitation, muscle jerking, and seizures or hypotension Use with care in patients with renal insufficiency, convulsive disorders, cardiac arrhythmias	Not recommended for management of chronic pain due to accumulation of toxic metabolite (normeperidine) that may cause CNS excitement, convulsions Metabolite limits use to less than 48 hours or 600 mg in 24 hours Oral administration NR for severe pain

Table 21. Examples of Opioid Analgesics (continued)

Generic Name	Indications	Usual Dosing Frequency	Routes of Administration[a]	Potential side effects[b]	Comments
Hydrocodone	Moderate to severe pain (e.g., trauma, back pain, postoperative pain, abdominal pain, dental pain)	4-6 h	PO	Mu agonist class side effects, precautions, warnings, and contraindications Combination hydrocodone + ibuprofen NR for OA or RA or for patients with NSAID hypersensitivity or other contraindication to NSAIDs	Available in combination with nonopioid Hydrocodone plus acetaminophen for moderate or moderately severe pain Hydrocodone plus ibuprofen combination product indicated for short-term (generally <10 days) management of acute pain (e.g., trauma, musculoskeletal and back pain, postoperative pain, abdominal pain, dental pain)
Codeine	Mild to moderately severe pain	4 h	PO, SC	Mu agonist class side effects, precautions, warnings, and contraindications Most common side effects are lightheadness, dizziness, shortness of breath, sedation, nausea, and vomiting	Used orally for mild-to-moderate pain, with limited use for severe pain Usually used in combination with nonopioid, which has an analgesic ceiling Codeine is a pro-drug and not all patients convert it to an active form to achieve analgesia

Sources: References 19-20, 22, 24, 50, 69, and 72-95. Product information (references 76-95) is from the Physicians' Desk Reference, 55th edition.[50]

[a]Although many of these opioids can be administered by intramuscular (IM) injection, IM administration is not recommended due to its multiple disadvantages (e.g., painful administration, unpredictable absorption, complications including tissue fibrosis and abscesses).[19]
[b]Many of these opioids only come in combination with a nonopioid (e.g., acetaminophen, NSAID). Therefore, additional contraindications, warnings, and side effects of that nonopioid drug apply. These combination products also are subject to a ceiling effect.
[c]Common side effects of mu agonists as a class include sedation, nausea, vomiting, constipation, pruritus (itching), and respiratory depression.[19] Less common side effects include euphoria or dysphoria. mu_1 receptors mediate supraspinal analgesia, and mu_2 receptors mediate spinal analgesia, physical dependence, and class side effects.[68]
[d]Mu agonists are generally contraindicated or need to be used with extreme caution in patients with known hypersensitivity to the drug, head injury or lesion associated with increased intracranial pressure, asthma and other respiratory conditions, or paralytic ileus.
[e]The 2001 Physicians' Desk Reference entry for Demerol® lists the dosing interval for meperidine as 3-4 hours, as necessary.[50] The 1992 Agency for Health Care Policy and Research Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1 lists the dosing interval for meperidine as 2-3 hours.[24]
CNCP: chronic noncancer pain; CNS: central nervous system; CR: controlled-release; EA: epidural anesthesia; IA: intrathecal anesthesia; IM: intramuscular; IR; immediate-release; IV: intravenous; MI: myocardial infarction; NR: not recommended; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; OTFC: oral transmucosal fentanyl citrate: PO: per os (oral); PR rectal; PRN: as needed; RA: rheumatoid arthritis; RF: renal failure; ROA: route of administration; SC: subcutaneous; SL: sublingual; TD: transdermal.

Table 22. Equianalgesic Dose Chart

Opioid	Equianalgesic Dose (mg) Oral	Parenteral
Morphine	30	10
Hydromorphone	7.5	1.5
Fentanyl	—	0.1
Oxycodone	20	—
Methadone	20 (acute) 2-4 (chronic)	10 (acute) 2-4 (chronic)
Meperidine	300 (NR)	75

Source: Reference 19.
NR: not recommended.

Table 23. General Management of Mu Agonist Opioid Side Effects

- Use preventive measures, especially in populations at high risk.
- Titrate drug doses slowly.
- If a symptom occurs, verify its cause (i.e., opioid side effect or another problem).
- If opioid-related side effects occur, consider changing the dosing regimen or route of administration to obtain relatively constant blood levels.
- Whenever possible, add (or increase dose of) nonopioid or adjuvant analgesic for opioid-sparing effect.
- Consider switching to another opioid.
- Add another drug that counteracts the effect (Table 24).
- Assume constipation will develop and treat it preemptively.

Sources: References 19, 24, 69, and 74.

Table 24. Specific Approaches to Management of Mu Agonist Opioid Side Effects

Side Effect	Precautions and Contraindications	Prevention and Management
Sedation	Elderly Concurrent sedating medications	General approach[a] plus: • Eliminate other nonessential medications with sedating effects • Consider use of mild stimulants during the day (e.g., caffeine) • Consider use of psychostimulant (e.g., methylphenidate) for persistent sedation, although exercise caution in combining psychoactive drugs in the elderly
Confusion Mental clouding	Elderly Preexisting CNS condition	General approach plus: • Eliminate other nonessential medications with CNS effects • Consider use of neuroleptics for persistent delirium
Respiratory depression	Opioid-naïve patients taking large opioid doses Head injury, lung disorder	General approach plus: • Monitor sedation level and respiratory status regularly, especially during first 24 hours of treatment in opioid-naïve patients • Stop opioid until respiratory depression resolves and reinstitute opioid at 75% of the previous dosage • Stop opioid and administer naloxone[b] for minimally responsive or unresponsive patients • Use spirometry and oxygen, as needed
Pruritus (itching)		General approach plus: • Consider administering diphenhydramine or hydroxyzine • Consider naloxone infusion titrated to the desired effect if other treatments fail
Nausea and vomiting	Concomitant conditions or treatments producing nausea and vomiting	General approach plus: • If nausea is due to stimulation of chemoreceptor trigger zone (central mechanisms), consider adding ondansetron, prochlorperazine, or hydroxyzine • If nausea is due to slowed gastric motility, consider adding metoclopramide • For chronic nausea, consider metoclopramide and/or other antiemetics
Constipation	Advanced age Immobility Abdominal problems or concurrent constipating medications	General approach plus: • Implement appropriate dietary changes • Assess regularly and use stool softeners and mild peristaltic stimulants for all patients on ATC opioids (prevention) • If no BM in a 48-hour period, add one or two additional agents (e.g., lactulose, milk of magnesia, senna) • If no BM in a 72-hour period, assess for (and treat) fecal impaction • If not impacted, try additional method (e.g., enema, mineral oil, magnesium citrate) • If impacted, use glycerine suppository or oil retention enema (as needed) to facilitate manual disimpaction, with appropriate analgesia

Sources: References 19, 24, 69, and 74.

[a]The general approach to managing side effects consists of changing the dosage or route of administration, trying a different drug in the same class, or adding a drug that counteracts the effect.

[b]For comatose patients, place endotracheal tube prior to administering naloxone. Also, titrate naloxone carefully to avoid profound withdrawal, seizures, and severe pain.[19]

ATC: around-the-clock administration; BM: bowel movement; CNS: central nervous system.

Table 25. Examples of Antiepileptic Drugs, Antidepressants, and Local Anesthetics[a]

Class	Generic Name	Indications	Uses in Pain[b]	Doage Forms and Routes of Administration	Potential Side Effects	Comments
Antiepileptic drugs	Gabapentin	Epilepsy	Neuropathic pains including PDN, PHN, RSD, deafferentation pain, thalamic pain, HIV-related neuropathy, phantom limb pain, migraine prophylaxis	Oral (capsules, tablets, solution)	Generally well tolerated Most common SE: somnolence, dizziness, fatigue, ataxia	First-line off-label treatment for neuropathic pain Well-established efficacy for PHN, PDN, and migraine headache prophylaxis Comparable efficacy to TCAs for PHN and PDN with superior side effect profile
	Carbamazepine	Epilepsy Trigeminal neuralgia	Neuropathic pains including TN, PHN, PDN, glossopharyngeal neuralgia, tabetic lightening pain, paroxysmal MS pain, PSP, dysethesia (spinal cord injury), post-laminectomy pain, cancer pain, phantom limb pain	Oral (tablets, ER tablets, suspension)	Most common SE: sedation, mental clouding, dizziness, nausea, unsteadiness Other SE: thrombocytopenia, liver damage, hyponatremia, rash	First FDA-approved anticonvulsant for the treatment of neuropathic pain Well-established efficacy in managing TN, PDN, PHN, but side effects limit use Baseline and regular monitoring of hematologic and liver function Monitor serum drug levels
	Divalproex sodium	Mania Epilepsy Migraine HA prophylaxis	Migraine (prophylaxis), TN, PHN	Oral (tablets)	Most common SE: sedation, nausea, vomiting, dizziness, HA Boxed warning for hepatic toxicity and pancreatitis Other SE: thrombocytopenia, inhibited platelet aggregation, hyperammonemia with or without lethargy, abnormal thyroid function tests, androgenization with hirsutism, amenorrhea, hair loss, polycystic ovaries	FDA approved for migraine HA prophylaxis Side effects limit wider use in chronic pain Monitor serum drug levels

Table 25. Examples of Antiepileptic Drugs, Antidepressants, and Local Anesthetics[a] (continued)

Class	Generic Name	Indications	Uses in Pain[b]	Doage Forms and Routes of Administration	Potential Side Effects	Comments
	Phenytoin	Epilepsy	PHN, PDN, TN, glossopharyngeal neuralgia, tabetic lightening pain, central pain, cancer pain, PSP, Fabry's disease	Oral (suspension, capsules, ER capsules, tablets) Parenteral (solution)	Most common SE: dose-related CNS effects (e.g., confusion, nystagmus, ataxia, decreased coordination) Other SE: lymphadenopathy, hepatotoxicity, hypersensitivity reaction, exfoliative dermatitis, gingival hyperplasia, toxicity and conduction disturbances at high blood levels	First anticonvulsant used for pain management Less commonly used now due to side effects and contradictory evidence of analgesic efficacy Monitor drug levels and watch for signs of toxicity (e.g., nystagmus, gait impairment, nausea, vomiting, sedation)
Antidepressants	Amitriptyline	Depression	Various types of CNCP (e.g., migraine and other HA, OA, chronic LBP, fibromyalgia), and neuropathic pain (e.g., PHN, PDN, central pain, chronic facial pain, cancer pain)	Oral (tablets, capsules, solution)	Common SE: sedation, anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention), orthostatic hypotension Other SE: arrhythmias, MI, stroke, worsening schizophrenic psychosis, hyperpyrexia, paralytic ileus Contraindications: status-post acute MI, hypersensitivity, concomitant MOAI use Use with caution in patients with seizures, urinary retention, angle-closure glaucoma, hyperthyroidism, CV disease, advanced age	Well-established analgesic efficacy Most used TCA for pain but least tolerated Produces the most anticholinergic side effects of all antidepressants Commonly associated with sedation, so administer at night Baseline ECG recommended and avoid use if QTc >440, AV block
	Nortriptyline	Depression	PDN, mixed neuropathic pains	Capsules, suspension	Common SE: insomnia, some sedation, anticholinergic effects Other SE and contraindications: see Amitriptyline	Better tolerated than amitriptyline due to less sedation and anticholinergic SE May cause insomnia, so administer during daytime
Local anesthetics (topical)	Lidocaine Lidoderm	Postherpetic neuralgia	PHN, PDN, stump pain, reflex sympathetic dystrophy, painful HIV-related neuropathy	Patch	Most common SE: localized reaction that usually resolves Less common SE: allergic and systemic reactions Use precautions in patients with severe hepatic damage and avoid eye exposure Contraindicated in patients with known sensitivity to LAs or for use on non-intact skin	Only FDA-approved treatment for PHN Anecdotal data suggest may be effective for other pain Low blood levels due to topical application Convenient and generally well tolerated

Table 25. Examples of Antiepileptic Drugs, Antidepressants, and Local Anesthetics[a] (continued)

Class	Generic Name	Indications	Uses in Pain[b]	Doage Forms and Routes of Administration	Potential Side Effects	Comments
	EMLA®	Local anesthesia on intact skin for procedures or superficial surgery on skin	Needle insertion, intravenous cannulation, spinal needle insertion, electrosurgery of cutaneous lesions, biopsies, PHN, other neuropathic pain	Cream, disc	Toxicity with repeated dosing, eye irritation, allergic reactions, methemoglobinemia	Placebo-controlled trials support efficacy in relieving acute pain associated with multiple procedures
Local anesthetics (other routes)	Bupivacaine	Local or regional anesthesia or analgesia for surgery; oral surgical and obstetrical procedures; and diagnostic and therapeutic procedures	Acute pain management: local infiltration, nerve blocks, epidural blocks, arthroscopy	Parenteral, epidural	Most common SE: dose-related CNS (e.g., anxiety, dizziness) and CV (e.g., arrhythmias, myocardial depression) effects Use with caution in patients with liver or heart disease due to risk of hepatic toxicity and arrhythmias Other SE: familial malignant hyperthermia	Moderate to fast acting, with long duration of action Better able to selectively block nociceptive nerve fibers Can be combined with opioids for epidural analgesia Only use 0.25% and 0.5% concentrations for obstetrical surgery
	Lidocaine	Local or regional anesthesia by infiltration techniques and IV regional anesthesia	Local infusion: local infiltration, nerve blocks, epidural blocks (e.g., postoperative pain, obstetrical pain), arthroscopy IV infusion: (rarely used) for some nociceptive and neuropathic pain, burn pain	IV, SC	Dose-related CV and CNS toxicity may progress to cardiac arrest, acidosis, and death with IV administration CNS SE: lightheadedness, dizziness, drowsiness, tinnitus, tremors, convulsions, unconsciousness CV SE: bradycardia, hypotension, CV collapse IV lidocaine contraindicated in patients with hypersensitivity to amide-type LAs, Adams-Stoke syndrome, severe heart block	Considered most widely used LA Can be combined with opioids for epidural analgesia IV use for pain normally reserved for pain refractory to other treatments due to risk of toxicity and unclear efficacy Topical lidocaine (see EMLA®, Lidocaine patch) is not associated with same side effects

Sources: References 19, 20, 50, and 104-142.

[a]This is a representative, not comprehensive, list.

[b]Most uses are off label.

AV: atrioventricular; CNCP: chronic noncancer pain; CNS: central nervous system; CV: cardiovascular; ECG: electrocardiogram; EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); ER: extended release; FDA: Food and Drug Administration; HA: headache; HIV: human immunodeficiency virus; IN: intranasal; IV: intravenous; LA: local anesthetics; LBP: lower back pain; MI: myocardial infarction; MOAI: monoamine oxidase inhibitor; MS: musculoskeletal; OA: osteoarthritis; PDN: peripheral diabetic neuropathy; PHN: postherpetic neuralgia; PSP: postsympathectomy pain; QTc: QT interval corrected for heart rate on ECG; RSD: reflex sympathetic dystrophy; SC: subcutaneous; SE: side effects; TCAs: tricyclic antidepressants; TN: trigeminal neuralgia.

but clinical trial evidence of its analgesic efficacy is limited and conflicting.[c,108-109] Clinical trial data support the use of carbamazepine in the treatment of trigeminal neuralgia, diabetic peripheral neuropathy, and postherpetic neuralgia,[112] but serious, albeit rare, side effects limit its use.[101] Recent data suggest that newer AEDs such as gabapentin are better alternatives to older AEDs.[101,110,112]

Placebo-controlled clinical trials have demonstrated that gabapentin provides effective analgesia comparable to TCAs for diabetic peripheral neuropathy[146-147] and postherpetic neuralgia;[114] it also has a more favorable side effect profile.[110,112] Data from a large study and a recent placebo-controlled trial also suggest that gabapentin effectively reduces the likelihood of migraine headaches.[115-116] Uncontrolled studies suggest that gabapentin also may be useful in the management of trigeminal neuralgia, central pain, phantom limb pain, and neuropathy associated with human immunodeficiency virus (HIV) infection.[120,148-150] Thus, many pain experts consider gabapentin a first-line treatment for neuropathic pain.[105,109,112,117-118]

iii. Side effects

Side effects of AEDs vary (Table 25). Common side effects of AEDs as a class include sedation, mental clouding, dizziness, nausea, or unsteadiness.[107] Initiating treatment at low doses and slowly titrating upward to optimal efficacy or toxicity diminishes the risk of these effects. Table 26 summarizes other ways to prevent and manage side effects. Less common but more serious adverse effects of some of the older AEDs include hematologic abnormalities, liver dysfunction, hypersensitivity reactions, and rash (Table 25). Thus, use of some of these agents requires close monitoring of drug levels, hematologic parameters, and liver function.[105] Unlike these older AEDs, gabapentin offers easy monitoring and relatively low toxicity (i.e., minimal drug-drug interactions and side effects).[101,110,112,119-120]

d. Antidepressants

i. Mechanism of action and effects

Antidepressants exhibit analgesic properties in animal models of nociceptive, inflammatory, and neuropathic pain, and some relieve chronic and neuropathic pain in humans.[151] These analgesic effects may reflect the ability of some antidepressants to block the reuptake of serotonin and norepinephrine in the CNS, thus increasing the activity of endogenous pain-modulating pathways.[152-154] Their analgesic actions do not depend on antidepressant activity,[155] and antidepressants are equally effective in patients with and without depression.[19] While analgesia may occur at lower doses and sooner than antidepressant activity, maximum efficacy may require high antidepressant doses and trial duration.

ii. Indications and uses

TCAs (e.g., amitriptyline, nortriptyline, imipramine) are adjuvant analgesics used to treat a variety of types of chronic (e.g., migraine, other headaches, low back pain, cancer pain, fibromyalgia) and neuropathic (e.g., painful diabetic neuropathy, postherpetic neuralgia, central pain, cancer-related) pain (Table 25).[107,122] All of these uses are "off-label." Although often considered most effective for continuous dysesthesias (i.e., burning pain or hypersensitivity), TCAs also may relieve lancinating neuropathic pain.[122,156-157]

Currently, TCAs are the only antidepressants with clearly demonstrated analgesic efficacy. Placebo-controlled clinical trial data suggest that TCAs provide effective[158-159] and comparable pain relief to AEDs for postherpetic neuralgia and diabetic neuropathy.[117,122,160-161] Amitriptyline has the best-documented analgesic effects but also the most side effects.[19] Intolerance of side effects, particularly among elderly patients, often limits TCA use.[118-119] Whereas newer antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors [SSRIs]) are generally better tolerated,[123-124] randomized controlled trials have yet to demonstrate analgesic efficacy.[d,123,149,162] There is preliminary evidence that venlafaxine, a new serotonin-norepinephrine reuptake inhibitor that lacks TCA side effects, may be efficacious in the treatment of neuropathic pain.[123,124] However, these results await formal evaluation in a randomized placebo-controlled trial.

iii. Side effects

TCA selection is largely based on patient characteristics and the drug side effect profile, because analgesic efficacy among individual

[c] Double-blind, placebo-controlled trials have demonstrated analgesic efficacy for diabetic neuropathy[143] and Fabry's disease,[144] although another small trial failed to demonstrate efficacy for diabetic neuropathy.[145]

[d] Data regarding the analgesic efficacy of SSRIs are conflicting[159,162-165] but generally suggest that SSRIs have less consistent analgesic effects than TCAs.[122,155,160,166]

Table 26. Approaches to Management of Antiepileptic Drugs, Tricyclic Antidepressants, and Local Anesthetic Side Effects

Side Effect	Populations at Increased Risk and Precautions	Prevention and Management
Sedation	Elderly	Titrate drug slowly and monitor drug levels, if recommended Consider changing dosing regimen or drug Administer drug at bedtime Eliminate other nonessential medications with sedating effects Consider use of mild stimulants during the day (e.g., caffeine) Consider use of psychostimulant (e.g., methylphenidate, dextroamphetamine) for persistent sedation, but exercise caution in elderly patients
Confusion Mental clouding	Elderly	Titrate drug slowly and monitor drug levels, if recommended Eliminate other nonessential medications with CNS effects Consider changing dosing regimen or drug
Dizziness/ orthostatic hypotension	Elderly	Titrate drug slowly and monitor drug levels, if recommended Encourage patient to change positions slowly and remain well hydrated Consider changing dosing regimen or drug if unmanageable
Anticholinergic effects	Elderly Patients with urinary retention or angle-closure glaucoma	Lower dose or change to drug with fewer anticholinergic effects Use sugarless hard candies or chewing gum for dry mouth and ensure regular dental examinations Use laxatives and stool softeners for constipation Consider bethanechol
Nausea and vomiting		Consider prochlorperazine or hydroxyzine
Cardiovascular effects	History of CAD, arrhythmias, or heart block	Obtain baseline ECG in all patients Monitor closely Be prepared to manage emergencies, including cardiac arrest

Source: Reference 19.

CAD: coronary artery disease; CNS: central nervous system; ECG: electrocardiogram.

TCAs is comparable.[122] Lethal side effects of TCAs are uncommon at dosages typically prescribed for pain, but cardiotoxicity with dangerous conduction abnormalities (arrhythmias) may occur.[125] Therefore, TCAs are relatively contraindicated in patients with conduction abnormalities (e.g., prolonged QT interval corrected for heart rate on the electrocardiogram), and a baseline electrocardiogram is recommended.[19]

Common and sometimes significant class effects of TCAs include sedation, orthostatic hypotension, and anticholinergic effects (i.e., dry mouth, blurred vision, constipation, urinary retention) (Table 25). Amitriptyline has the strongest sedative and anticholinergic side effects, so bedtime administration is recommended.[19] Elderly patients are at greatest risk for some side effects, including sedation and orthostatic hypotension. Nortriptyline is less likely than amitriptyline to produce these effects,[19] so it may be a more appropriate initial choice for an elderly patient. Nortriptyline should be administered during the day if it produces insomnia.[19] Table 26 summarizes some ways to prevent and manage common TCA side effects.

e. Local anesthetics

i. Mechanism of action

LAs are another type of adjuvant analgesic. These drugs block sodium channels and inhibit the generation of abnormal impulses by damaged nerves to exert their peripheral analgesic effects.[167] When used systemically, they do not produce conduction block (anesthesia) as they do with local injection and topical application but may suppress aberrant electrical activity in structures associated with pain.[107,168-169]

ii. Indications and uses

LAs are used to manage acute and chronic pain (Table 25) and are administered in several ways for different purposes. Topical application provides localized analgesia for a painful procedure or condition with minimal systemic absorption or side effects.[106] EMLA® (Eutectic Mixture of Local Anesthetics [lidocaine and prilocaine]) is a topically applied LA used to prevent pain associated with various procedures (e.g., needle insertion, intravenous cannulation, superficial skin surgery).[170] Placebo-controlled trial data suggest that EMLA® effectively relieves acute pain associated with procedures, including

venipuncture,[171-173] spinal needle insertion,[174] and excisional biopsy or curretage of cutaneous lesions.[175-176]

Topical LAs are also used to treat neuropathic pain.[106] The lidocaine patch (Lidoderm®) is the first FDA-approved treatment for postherpetic neuralgia.[177] A large, multicenter, placebo-controlled trial showed that it relieved pain in patients with long-standing postherpetic neuralgia and mechanical allodynia.[178] Other controlled studies suggest that both the patch and gel forms of lidocaine significantly reduce postherpetic neuralgia, produce no significant side effects, and are easy to use.[106,179-180] Anecdotal evidence suggests that the lidocaine patch also may be useful for other neuropathic pain, including diabetic neuropathy, HIV-related neuropathy, complex regional pain syndrome, postmastectomy pain, postthoracotomy pain, and stump pain.[106,181]

LAs also can be used in more invasive approaches collectively referred to as regional anesthesia. For example, LAs (e.g., lidocaine, bupivacaine, ropivacaine) can be injected into tissue (local infiltration), around nerves (i.e., nerve blocks), or into various spaces surrounding the spine (i.e., epidural and intrathecal analgesia). Epidural blocks with LAs with or without opioids play an important role in managing postoperative and obstetrical pain.[107] Nerve blocks with LAs sometimes are used to manage chronic pain (e.g., occipital headaches, lower back pain), and LAs can be combined with other agents (e.g., corticosteroids, saline) for trigger point injections.[182]

Rarely, intravenous LAs (e.g., lidocaine) are used to manage neuropathic pain, arthritis, poststroke pain, or headache[107,126-128] or, somewhat more often, to anesthetize an upper extremity. Oral LA-type antiarrhythmic drugs (e.g., flecainide, mexiletine) have, in some cases, been used to manage neuropathic or cancer pain.[129-130] However, use of these drugs is generally not recommended, because they may cause serious side effects and evidence of their analgesic efficacy is limited and conflicting.[107]

iii. Side effects

Major dose-dependent toxicities associated with systemic administration of LAs include CNS (e.g., dizziness, tremor, paresthesias, encephalopathy, seizures) and cardiovascular (e.g., conduction disturbances, depression of myocardial function) side effects (Table 25). Thus, treatment in some patient populations is contraindicated, and all patients need to be closely monitored (e.g., with plasma drug levels, electrocardiography). In contrast, topical LAs are well tolerated with a low incidence of side effects.[106] As serum concentrations of the LA remain low, even with chronic use,[177] topical LAs can even be used in patients with cardiovascular disease.

f. Other

Nonopioids and opioids are used to manage most nociceptive pain, although LAs are also useful for postoperative pain management. AEDs, TCAs, and LAs are the mainstay of treatment for neuropathic pain. However, this does not account for all drugs used in pain management. Table 27 summarizes information about other drugs and drug classes used for specific conditions or clinical circumstances. These include drugs used for arthritis pain (e.g., capsaicin), cancer and inflammatory pain (e.g., corticosteroids), migraine headaches (e.g., "triptans," beta-blockers), chronic pain (e.g., tramadol, baclofen) and pain refractory to other treatments (N-methyl-D-aspartate antagonists).

3. General Principles of Analgesic Therapy

Some principles of analgesic therapy are drug specific. However, some general principles guide all pharmacologic treatment of pain:

a. Identify and treat the source of the pain.

Whenever possible, identify and treat the underlying cause of the pain. However, pain management can begin before the source of the pain is determined.

b. Select the simplest approach to pain management.

Although invasive methods are sometimes required, most pain can be relieved via simple methods. Cost of treatment is also a consideration in some cases.

c. Select an appropriate drug.

Individualization of a pain management regimen begins with selection of an appropriate drug. Factors that guide this process include:[19-20]

- Characteristics of the pain (e.g., duration, intensity, quality)
- Characteristics of the agent (e.g., analgesic ceiling, expected time of onset and duration

Table 27. Other Drugs Used in Pain Management

Class	Generic Name	Indications	Uses in Pain	Routes of Administration and Dosage Forms	Potential Side Effects	Comments
Topical analgesics	Capsaicin	Arthritis, neuropathic pain	PHN, PDN, OA, RA	Topical	Mild to severe burning on application	RCT have shown efficacy for OA and RA but mixed results for PDN and PHN Available OTC
Corticosteroids	Dex-amethasone	Multiple, including endocrine, rheumatic, collagen-vascular, dermatologic, allergic, ophthalmologic, respiratory, oncologic, hematologic disorders	Cancer-related pain (e.g., malignant epidural spinal cord compression, raised intracranial pressure, superior vena cava syndrome); symptoms of bowel obstruction; pain related to musculoskeletal conditions (e.g., OA, RA, bursitis, tendonitis)	PO (tablets, elixir), injectable form	Contraindicated in patients with systemic fungal infections or hypersensitivity to drug Drug-induced adrenocortical insufficiency, mask signs of infection, eye problems (e.g., glaucoma, cataracts), increased blood pressure, electrolyte/body fluid imbalances, increased risk of infection, psychiatric disturbances, GI problems (e.g., ulceration, bleeding), osteoporosis, pathological fractures, withdrawal syndrome with sudden discontinuation	Generally tolerated for short-term treatment, but toxicities often arise with prolonged high-dose therapy Dosage must be tapered before discontinuation to prevent withdrawal symptoms
	Methylpred-nisolone			PO		
Mixed mu agonist opioid and NE/5-HT reuptake inhibitor	Tramadol	Moderate to moderately severe pain	Types of CNCP (e.g., OA, fibromyalgia, PDN, LBP)	PO	Common SE: dizziness, nausea, constipation, headache, sedation Uncommon SE: increased risk of seizures with high doses (>400 mg/day) or history of seizure disorder; rare anaphylactoid reaction	Contraindicated in patients with hypersensitivity or acute drug intoxication Comparable pain relief to acetaminophen + codeine May have lower potential for abuse than opioids
Selective 5-$HT_{1B/1D}$ receptor agonist	Zolmitriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets)	Dizziness, drowsiness, nausea, atypical or pressure sensations Certain contra-indications (see comments)	Effective abortive treatment for migraine Contraindicated/NR in patients with: • Ischemic heart (e.g., MI) or cerebrovascular (e.g., stroke) disease • Uncontrolled HTN • Hemiplegic or basilar migraine • Hypersensitivity • Recent ergots or MAOI use

Table 27. Other Drugs Used in Pain Management (continued)

Class	Generic Name	Indications	Uses in Pain	Routes of Administration and Dosage Forms	Potential Side Effects	Comments
	Rizatriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets, orally disintegrating tablets)	Warm/cold sensations, diarrhea, nausea, flushing Certain contraindications: see Zolmitriptan	
	Sumatriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of cluster headache episodes (SC form only)	PO (tablets), IN, SC	Atypical (e.g., flushing, tingling, warmth) and pressure sensations; nausea Certain contraindications: see Zolmitriptan	Intranasal sumatriptan also contraindicated in patients with severe hepatic impairment
Beta-blockers	Propranolol	HTN, MI, migraine prophylaxis, essential tremor, HSS, pheochrom-ocytoma	Migraine prophylaxis	PO (tablets, LA capsules), injectable	Common SE: bradycardia, hypotension Other SE: lethargy, depression Contraindicated in patients with cardiogenic shock, heart block, bronchial asthma, CHF Use caution in patients with history of CHF or angina, diabetes, hyperthyroidism	Effective migraine prophylaxis
$GABA_B$ receptor agonists	Baclofen	Spasticity	Intraspinal baclofen is used for some chronic neuropathic pain refractory to other treatments	Intraspinal	Abrupt discontinuation can trigger withdrawal symptoms, including delirium and seizures	Useful for pain caused by spasticity
NMDA receptor antagonists	Ketamine	General anesthetic	Neuropathic pain (e.g., phantom limb pain), cancer pain, procedural pain (rarely used)	Parenteral	CNS side effects: sedation, ataxia, delirium, hallucinations, psychosis, nightmares, dysphoria Sedation is most common side effect at low doses	Rarely used due to debilitating CNS side effects New NMDA receptor antagonists are in development

Sources: References 19, 50, 104-106, 183-200.
5-HT: 5-hydroxytryptamine (serotonin); $5\text{-}HT_{1B/1D}$: 5-hydroxytryptamine receptor subtypes $_{1B/1D}$; CHF: congestive heart failure; CNCP: chronic noncancer pain; CNS: central nervous system; $GABA_B$: γ-aminobutyric acid (GABA) type B receptor; GI: gastrointestinal; HSS: hypertrophic subaortic stenosis; HTN: hypertension; LA: long-acting; LBP: lower back pain; MAOI: monoamine oxidaase inhibitor; MI: myocardial infarction; NE: norepinephrine; NMDA: N-methyl-D-aspartate; NR: not recommended; OA: osteoarthritis; OTC: over-the-counter (nonprescription); PDN: peripheral diabetic neuropathy; PHN: postherpetic neuralgia; PO: per os (oral); RA: rheumatoid arthritis; RCT: randomized controlled trials; SC: subcutaneous; SE: side effects.

of analgesia, available routes of administration, dosing interval, side effects, potential for accumulation of toxic metabolites, potential for addiction)
- Patient factors (e.g., age, coexisting diseases, other medications, preferences, response to previous treatments).

d. Establish a management plan.

The next step is to establish a management plan, which may include the later addition of other drugs. Use of several analgesics in combination offers several advantages. It may:
- Allow use of lower doses of some agents, thus reducing the risk of side effects
- Inhibit nociceptive processing at multiple (i.e., peripheral and central) levels, thus enhancing analgesia
- Facilitate treatment of pain in patients who do not respond to a single agent.

Common acceptable combination regimens include: 1) a nonopioid plus an opioid or 2) a nonopioid plus an opioid plus an adjuvant analgesic.[20]

e. Select a route of administration.

No single route of drug administration is appropriate for all clinical situations. Patient factors (e.g., preferences, comfort, convenience, GI function) and drug characteristics (e.g., absorption, half-life) influence the selection of an appropriate route. Table 28 reviews advantages and disadvantages of various routes of administration.

Oral administration of drugs, especially for chronic treatment, is generally preferred because it is convenient, flexible, and associated with stable drug levels.[19] Although often used, IM administration has multiple disadvantages (e.g., pain, erratic absorption, fluctuating drug levels, tissue fibrosis), thus should not be used.[19,24] Intravenous (IV) administration provides a rapid onset of pain relief and, along with rectal, sublingual, and subcutaneous administration, is useful in patients who cannot take medications by mouth. Continuous infusions produce consistent drug blood levels but are expensive, require frequent professional monitoring, and may limit patient mobility.[19] Transdermal administration is a convenient alternate means of continuous drug delivery that does not involve needles or pumps.[202] Some data suggest that some patients prefer transdermal opioid (fentanyl) to sustained-release oral morphine.[203-205]

Table 29 describes some "high-tech" methods of providing analgesia, including patient-controlled analgesia (PCA), intraspinal (epidural and intrathecal) drug administration (neuroaxial blockade), and other interventional techniques. PCA permits administration of a small dose of drug upon patient command and is especially useful in patients expected to require opioids over a period that exceeds 12 hours. It has mostly been used for IV administration of opioids for acute pain (e.g., postoperative pain), but newer PCA techniques include subcutaneous and epidural drug administration.[208] Interventional methods of analgesia include tissue infiltration (e.g., trigger point injections with local anesthetics), sensory nerve blocks, sympathetic blocks, spinal injections (e.g., epidural injections of corticosteroids, caudal blocks, nerve root injections), and continuous spinal analgesia (e.g., infusion of opioids, clonidine, baclofen) (Table 29). Nerve blocks can be used for diagnostic, prognostic, and therapeutic purposes.

f. Titrate the dose.

It may be necessary to titrate the dose of an analgesic to achieve an optimal balance between pain relief and side effects. The goal is to use the smallest dosage necessary to provide the desired effect with minimal side effects.[19] Nonopioids have a ceiling effect and may cause significant toxicity at high doses. However, most opioids do not have an analgesic ceiling, so the dosage can be titrated upwards until pain relief occurs or limiting side effects develop.

g. Optimize administration.

Medications can be administered around-the-clock (ATC) after an optimal dose over a 24-hour interval is determined.[19] Experts recommend ATC dosing for patients with continuous pain, because it provides superior pain relief with fewer side effects.[19] It also helps to break the undesirable undermedication-overmedication cycle that often develops with use of PRN medications alone. However, a short-acting, rapid-onset PRN medication should be used to manage breakthrough pain (i.e., pain that "breaks through" pain relief provided by ongoing analgesics). PRN dosing is also useful for intermittent pain, but patients need to be taught to request pain medication early, before the pain becomes severe.

h. Watch for and manage side effects.

Patients with new or altered analgesic regimens should be observed and assessed for side

Table 28. Routes of Administration

Route	Definition and Notes	Drug Types	Comments
Oral	By mouth (per os) Requires functioning GI tract, intact swallowing mechanism, sufficient GI tract for absorption to occur	Nonopioids, opioids, adjuvant analgesics	Advantages: convenient, noninvasive, cost-effective, flexible, less discomfort than injections with comparable efficacy Disadvantages: requires functional GI system; slow onset of action and relatively delayed peak effects; requires patient compliance
Rectal	Insertion of suppository into rectum	Nonopioids, opioids	Useful in patients who cannot take medications by mouth Any opioid may be compounded for rectal administration
Intramuscular	Injection into large muscle (e.g., gluteus or vastus lateralis)	Some nonopioids, opioids	IM administration should not be used, especially for chronic treatment, due to multiple disadvantages: • Painful injections • Wide fluctuations in drug absorption make it difficult to maintain consistent blood levels • Rapid fall-off of action compared with PO administration • Chronic injections may damage tissue (fibrosis, abscesses) IV and SC injections are appropriate alternatives
Intravenous	Injection into vein; may be single or repetitive bolus or continuous infusion with or without PCA	Some nonopioids, opioids, adjuvant analgesics	IV is most efficient ROA for immediate analgesia and permits rapid titration IV bolus produces rapid onset of effect, but shorter duration of action than IM; not recommended for drugs with long half-lives Continuous IV infusion provides steadier drug blood levels, which maximize pain relief while minimizing side effects
Subcutaneous	Placement of drug just under skin with small needle Continuous SC infusion can be obtained with a small needle	Some opioids	Advantages: produces steady blood levels; time until onset of effect is comparable to IM administration and effects are longer lasting, with less painful administration; cheaper than IV administration; obviates need for GI function Disadvantages: slower onset and offset and lower peak effects than IV administration, time consuming, often disliked by patients
Topical	Applied directly to the skin, where the drug penetrates	NSAIDs, local anesthetics (e.g., lidocaine patch and gel, EMLA®), capsaicin	Advantages: local effect (i.e., no significant serum levels) limits side effects to local reactions; no drug-drug interactions; easy to use, no titration needed Disadvantages: may cause local skin reactions
Transdermal	Absorbed through skin with gradual release into the systemic circulation	Some opioids, adjuvant analgesics	Advantages: convenient, noninvasive, provides prolonged, relatively stable analgesia Disadvantages: delayed onset of action with first dose, drug absorption influenced by internal or external heat
Oral transmucosal	Delivery of drug to mouth, including sublingual (under tongue) and buccal/gingival administration	Some opioids	Advantages: easy, requires little staff supervision; avoids significant liver metabolism associated with oral opioids Disadvantages: variable absorption, bitter taste, dose is limited
OTFC	Fentanyl incorporated into a sweetened matrix on a stick for consumption	Fentanyl	Some absorption via oral mucosa, but most via GI tract; yields higher drug levels and better bioavailability than oral fentanyl
Intranasal	Small aerosol device placed inside nostril that delivers a calibrated dose of a drug	Butorphanol, sumatriptan	Takes advantage of rich blood supply to nose and also avoids significant liver metabolism associated with some drugs
Intraspinal	Epidural and intrathecal administration (see Table 29)		
Other (sublingual, vaginal)	Placement of drug under the tongue (sublingual) or in the vagina	Opioids	Most opioids can be absorbed sublingually or vaginally in patients who have problems such as impaired swallowing, short gut syndrome, or poor IV access

Sources: References 19, 20, 69, and 201.

EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); GI: gastrointestinal; IM: intramuscular; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; OTFC: oral transmucosal fentanyl citrate; PCA: patient-controlled analgesia; PO: per os (oral); ROA: route of administration; SC: subcutaneous.

Table 29. PCA and Regional Anesthesia

Route	Definition	Example Drug Types	Comments
PCA	Use of infusion pump that allows patient to self-administer small doses of analgesics via one of several routes (e.g., IV, SC, epidural)	Opioids (e.g., morphine, hydromorphone, fentanyl, meperidine), some NSAIDs	Used for numerous surgeries (e.g., C-section, abdominal, orthopedic) and medical conditions (cancer pain, sickle cell crisis, burn pain, HIV pain, pancreatitis, kidney stones, fractures) Advantages: less delay in onset of analgesia than PRN dosing Compared with IM, improved analgesia with smaller doses of opioids and fewer side effects Disadvantages: Patient must understand technique, so less useful in some clinical populations
Single or repetitive epidural bolus	Injection or infusion of agent into the epidural space via insertion of a needle (single bolus) or catheter (repetitive bolus)	Opioids (e.g., morphine, fentanyl hydromorphone), local anesthetics (e.g., bupivacaine, ropivacaine), corticosteroids, clonidine, baclofen	Used for diagnostic and therapeutic nerve blocks; the latter include surgeries (e.g., C-section, gynecologic, urological surgeries) Advantages: simple, no need for infusion device, delivery to site close to site of action (spinal cord) permits more intense analgesia (greater analgesia for given drug) Disadvantages: limited number of suitable agents, higher incidence of side effects, requires personnel to reinject catheter, higher risk of catheter contamination, does not permit PCA
Continuous epidural	Continuous infusion of agent(s) into the epidural space via a catheter. A long-term catheter can be tunneled under the skin or surgically implanted for long-term pain management (e.g., cancer pain, CNCP)	Opioids, local anesthetics	Used for acute pain (e.g., postoperative, obstetrical, posttraumatic pain) and chronic pain (e.g., cancer pain, neuropathic pain) Advantages: permits concomitant use of local anesthetic and shorter-acting opioids, eliminates need for catheter reinjection, reduces rostral spread of analgesia, less risk of catheter contamination, greater potency than systemic administration Disadvantages: Potential for catheter migration and side effects (e.g., of skin and subcutaneous tissue around catheter site; rarely, hematoma, abscess, or meningitis)
PCEA	Continuous infusion of drugs into epidural space, controlled by a patient-operated infusion pump	Opioids	Allows patient to manage dynamic changes in pain related to activity
Bolus or continuous intrathecal (spinal)	Injection or infusion of agent into the subarachnoid space via insertion of a needle (single bolus) or catheter (repetitive bolus); an indwelling intrathecal catheter can be placed for long-term analgesia to reduce the risk of infection	Opioids (e.g., morphine, hydromorphone, fentanyl), local anesthetics (e.g., lidocaine, bupivacaine, mepivacaine)	Uses include cancer pain (regionalized pain below T1), neuropathic pain Single bolus more commonly used for acute pain due to difficulty in maintaining indwelling intrathecal catheters. May be cost-effective for patients with cancer or CNCP Advantages: provides intense analgesia at lower doses than systemic administration Disadvantages: can be difficult to titrate drug effect, risk of infection and other side effects Onset and duration of effect reflect lipid solubility of agent; greater effects of drug at given dose than with systemic administration
Local infiltration	Infiltration of various body structures with local anesthetics and/or corticosteroids	Local anesthetics (e.g., bupivacaine), corticosteroids	Used for acute pain (e.g., postoperative pain, postoperative joint pain, acute bursitis, tendonitis, muscle spasm) and chronic pain (e.g., painful scars, neuromata, trigger points for myofascial syndromes, arthritis, facet syndrome)
Spinal nerve block	Blockade of spinal neurons outside the spinal canal in the paravertebral region or anywhere along its course	Local anesthetics	Includes cervical spinal blocks, occipital blocks, thoracic spinal blocks, lumbar and sacral spinal nerve blocks, sympathetic blockade Used for severe acute or chronic pain (e.g., postoperative, posttraumatic, postamputation, PVD, cancer pain, visceral pain, CRPS, neuralgias)
Topical application	Application of local anesthetics to skin (e.g., patch, gel, cream, paste)	Topical local anesthetics (e.g. lidocaine, EMLA®); other local anesthetics (e.g., cocaine, benzocaine)	Oral agents used for pain in mucous membranes of mouth Topical anesthetics used for procedural pain (EMLA®) and some chronic pain (e.g., lidocaine patch or gel for postherpetic neuralgia)

Sources: References 19, 69, 206-207.

C-section: Cesarean section; CNCP: chronic noncancer pain; CRPS: chronic regional pain syndrome; EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); HIV: human immunodeficiency virus; IM: intramuscular; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; PCA: patient-controlled analgesia; PCEA: Patient controlled epidural analgesia; PRN: as needed; PVD: peripheral vascular disease; SC: subcutaneous.

effects as well as pain relief. Tables 20, 23, 24, and 26 review some specific approaches to managing common side effects of nonopioid, opioid, and adjuvant analgesics. The general strategy to managing side effects consists of:[19]

- Changing the dosage or route of administration (to achieve stable drugs levels),
- Trying a different drug within the same class, and/or
- Adding a drug that counteracts the effect (e.g., antihistamine for pruritus, laxative for constipation).

Combination therapy can alleviate some side effects. For example, adding a nonopioid or adjuvant analgesic to an opioid regimen may allow use of a lower dose of the opioid. Severe side effects, on occasion, may require administration of an opioid antagonist (e.g., naloxone for opioid-induced respiratory depression).[19] Use of agents with potentially hazardous metabolites (e.g., meperidine) should be restricted to short-term treatment.[19]

i. Differentiate among tolerance, physical dependence, and addiction and appropriately modify therapy.

Section I.E.5 reviews the definitions of tolerance, physical dependence, and addiction recently recommended by the American Society of Addiction Medicine (ASAM), the American Academy of Pain Medicine (AAPM), and the American Pain Society (APS).[209] Confusion regarding these terms is common and adversely influences pain management.

Tolerance normally occurs with use of certain agents (e.g., opioids). Its earliest sign is a decrease in the duration and/or degree of pain relief, which can be managed by increasing the drug dose and/or frequency of administration.[19] Combining opioids with nonopioids, or switching to a lower dose of another opioid, may delay the development of opioid tolerance.[19] However, the latter approach requires a great deal of care and significant expertise.

Signs of physical dependence include the appearance of an abstinence syndrome with abrupt cessation or diminution of chronic drug administration.[19] The nature and time of onset of this syndrome vary with drug actions and half-life. Slow tapering of the drug (e.g., 10-15% reduction in dosage per day or every other day) usually avoids the appearance of an abstinence syndrome.[210]

Although not usually encountered in patients without a history of preceding drug abuse, the administration of some drugs (e.g., opioids) may cause addiction. Signs of drug craving and/or drug-seeking behavior (e.g., missed appointments with after-hour calls for prescription renewals; solicitation of prescriptions from multiple physicians; reports of lost, destroyed, or stolen medications; selling and buying drugs off the street)[19] should alert the clinician to such a possibility. However, diagnosing addiction requires extreme caution. Similar behaviors, called "pseudoaddiction," sometimes occur in patients who are not receiving adequate pain management (e.g., doses of opioids too low or infrequent).[211] It is critical that addiction be diagnosed because it is a treatable but serious condition and failure to treat it will hinder efforts to manage pain.

j. Avoid use of placebos to treat pain.

Placebos are sometimes used to assess whether pain is responsive to sympatholysis or other interventions. However, the deceptive use of placebos to treat pain is considered unethical and inappropriate.[19]

B. Nonpharmacologic Treatments for Pain

Pharmacologic approaches to pain management are the mainstay of treatment for acute pain and cancer pain and are increasingly being used to manage chronic noncancer pain (CNCP). However, optimal pain management also includes psychological, physical rehabilitative, and in some cases, surgical treatment strategies. For example, the 1992 Agency for Health Care Policy and Research clinical practice guideline on acute pain management recommends cognitive-behavioral approaches (e.g., patient education, simple relaxation, imagery, hypnosis, and biofeedback) and physical therapeutic agents and modalities (e.g., superficial heat or cold, massage, exercise, immobility, and electroanalgesia) as part of the management of acute pain.[24]

Nonpharmacologic strategies should supplement, but not replace, the use of medications.[24] In addition to supplementing the pain-relieving effects of analgesics, nonpharmacologic approaches offer other advantages. For example, they can improve mood, reduce anxiety, increase a patient's sense of control, strengthen coping

abilities, assist with sleep, relax muscles, and improve quality of life.[212-213] Factors that influence the choice of a nonpharmacologic approach to pain management include the pain type, duration, and severity; the patient's preferences, coping skills, and capabilities; the availability of support (e.g., family members); the availability of care within the community; and cost.

1. Psychological Approaches

Psychological interventions used in pain management include contingency management, cognitive behavioral therapy, biofeedback, relaxation, imagery, and psychotherapy. Table 30 defines these terms and describes potential uses of these methods. Some methods (e.g., relaxation, imagery) are simple and can be taught quickly, whereas others require more time. Patient education materials (e.g., printed instruction sheets, audiotapes) can supplement, but not replace, clinician efforts to instruct patients in these methods.[24]

Patients in whom psychological interventions may be most appropriate include those who express interest in such approaches, manifest anxiety or fear, have inadequate pain relief after appropriate pharmacologic interventions, or experience chronic or recurrent pain.[24] When pain is acute, psychological preparation (such as preparation for surgery or for an invasive procedure) or psychological intervention such as relaxation may help to control the affective dimension of pain.[218] This, in turn, helps minimize the biological stress response that the patient experiences as well as emotional distress and suffering.[215] When pain is chronic, learning history and operant conditioning (Table 30) sometimes contribute to the persistence of pain and disability, and counterproductive beliefs may impede a positive response to medical intervention.[214] Therefore, psychological methods are typically an integral part of the interdisciplinary approach to the management of chronic pain. Because such management usually involves rehabilitation, psychological approaches are typically integrated with rehabilitation efforts built around physical therapy.

Psychologists rarely treat pain directly but rather work with other health care professionals to integrate psychological principles into the interdisciplinary management of pain. For example, a psychologist can improve communication between a health care provider and patient or work with a clinician to alter the characteristics of a treatment regimen (e.g., complexity, dosing frequency, cost). Such psychological interventions may help assess and enhance patient adherence with treatment (e.g., medications, physical therapy), thus increasing the probability of successful management.[e,215] Unfortunately, psychological approaches to pain management are not used as often as they should be,[215] due to a variety of reasons (e.g., lack of awareness of the role of psychological factors in the response and adaptation to pain, time constraints, reimbursement policies).

2. Physical Rehabilitative Approaches

Physical rehabilitative methods of pain management are appropriate for many types of pain and are essential in patients with CNCP. In addition to relieving pain, such methods can reduce fear and anxiety, improve physical function, and alter physiological responses to pain. Treatments used in physical rehabilitation include stretching, exercises/reconditioning (to improve strength, endurance, and flexibility), gait and posture training, and attention to ergonomics and body mechanics.[182] Other noninvasive physical treatments for pain include thermotherapy (application of heat), cryotherapy (application of cold), counter-irritation, and electroanalgesia (e.g., transcutaneous electrical stimulation) (Table 31).[182] In some cases, patients choose to pursue non-allopathic (alternative treatments) such as acupuncture or therapeutic massage.

3. Surgical Approaches

Most pain can be managed by simple noninvasive methods. However, more invasive approaches, including surgery, are sometimes needed. Orthopedic approaches to pain management include both nonsurgical ("conservative") approaches and various surgeries (e.g., total joint replacement, laminectomy, spinal fusion).

[e] One reason that medical interventions sometimes fail or minimally succeed is poor patient adherence to treatment regimens. Estimates of the prevalence of medication nonadherence for the population as a whole are relatively high (30% to 60%), and patients tend to underreport poor adherence and overreport good adherence.[219] Although few studies have addressed the prevalence of nonadherence with pain medication regimens, it appears to be a problem.[220-222]

Neurosurgical procedures for managing pain include neurolysis (i.e., injection of a chemical or application of heat or cold to destroy neural tissue), neuroaugmentation procedures, and neuroablative surgeries (i.e., disruption of neural signals and/or removal of neural structures associated with pain).[229] For example, microvascular decompression of the trigeminal nerve is sometimes used to manage trigeminal neuralgia.

Although beyond the scope of this monograph, a variety of other surgical approaches to pain management exist. Other sources (e.g., Bonica's Management of Pain, 3rd ed.) provides complete coverage of these methods.

Table 30. Examples of Psychological Methods Used to Manage Pain

Intervention	Definition	Purpose/Goals	Uses
Patient education	Provision of detailed information about disease or interventions and methods of assessing and managing pain (e.g., preoperative instruction about importance of deep breathing, coughing, and ambulating postoperatively; teaching patients with chronic pain about what may aggravate and relieve pain)	Can reduce pain, analgesic use, and length of hospital stay	Postoperative pain, chronic pain
Contingency management[a]	CM involves the manipulation of environmental consequences of pain behavior in a way that helps patients to modify their behavior; it involves use of social reinforcers to increase "well behavior" (e.g., exercise, non-medical conversation) and decrease "sick role" behavior	Refers to methods not for treating the pain per se but rather helping patients to change behaviors Studies suggest that CM effectively reduces pain	Chronic pain
CBT	CBT combines cognitive therapy techniques (e.g., attention diversion) with behavioral techniques (e.g., relaxation, assertiveness training); there are two major CBT subtypes: cognitive restructuring and coping skills training	Helps patients alter their perceptions or labeling of pain (i.e., decrease negative thoughts, emotions, and beliefs), increase sense of control, and decrease maladaptive behaviors	Chronic pain especially, but also useful for acute pain
Cognitive restructuring	Type of CBT in which patients are taught to monitor and evaluate negative thoughts	The goal is to generate more accurate and adaptive thoughts	Chronic pain
Coping skills training	Type of CBT that helps patients develop coping skills, which includes relaxation and imagery techniques, adaptive coping self-statements, and group psychotherapy	Directed at helping patients to develop skills to manage pain and stress	Multiple types of pain (see below)
Relaxation with imagery	Includes progressive muscle relaxation, imagery, visualization, and meditation One of most widely used nonpharmacologic treatments for pain that can increase focus on feelings of well-being as well as diminish tension, anxiety, depression, and pain-related inactivity.[b]	Relaxation decreases patient's focus on pain, muscle tension, and autonomic and emotional arousal; imagery provides a competing cognitive focus, which can block the perception of pain	Postoperative pain, chronic headache, chronic LBP, cancer pain, arthritis pain, labor pain, TMD
Hypnosis	Technique in which a patient's susceptibility to suggestion is heightened, facilitating modification of memory and perception; hypnosis can be used alone or as a means of enhancing the effectiveness of another clinical intervention	Hypnosis may provide comfort and reduce anxiety and suffering associated with acute, recurrent, and chronic types of pain; it reduces cortical activation associated with painful stimuli	Postoperative, burn, dental, labor, cancer, procedural, neuropathic, and musculoskeletal pain; headache
Distraction	Includes repeating reaffirming phrases, singing, talking, etc., to distract attention from unpleasant awareness of pain; in patients with CNCP, it also may include social and recreational activities	The goal is for the patient to actively occupy his or her attention with an activity or topic other than pain	Multiple acute and chronic types of pain
Biofeedback	Patient learns to take voluntary control over physiological body activities by receiving input (e.g., visual or auditory cues) about these activities (e.g., heart beat, muscle tension, skin temperature)	Directed at teaching a patient how to take control of body responses via mental activity	Most support for use with vascular HA; also used for chronic LBP and other HA, myofascial pain, rectal pain
Psychotherapy	Treatment for a mental illness or maladaptive behaviors that involves a therapist establishing a relationship with a patient to achieve certain goals; includes individual (supportive and dynamic), group, and family psychotherapy	Goals of psychotherapy include modifying symptoms, changing maladaptive behaviors, and promoting growth and development	Chronic pain, cancer pain, pain associated with HIV infection

Sources: References 24, 72, and 214-218.

[a]The terms "contingency management" and "operant conditioning" are used interchangeably. Overlap exists between CM and CBT, but CM focuses more on modifying behavior and CBT helps more with altering patient perceptions or labeling of sensations.[214]

[b]These methods can be taught quickly but patients do best with encouragement from health care professionals and family members. Audiotapes and printed materials also can be helpful.[24]

CBT: cognitive-behavioral therapy; CM: contingency management; CNCP: chronic noncancer pain; HA: headache; HIV: human immunodeficiency virus; LBP: low back pain; TMD: temporomandibular disorder.

Table 31. Examples of Physical Methods Used to Manage Pain

Intervention	Definition	Purpose/Goals	Examples of Uses
Stretching	Gentle exercise to improve flexibility	Improve ROM, function, comfort	Arthritis, LBP, fibromyalgia, myofascial pain syndrome
Exercise/ reconditioning	Reconditioning exercises can improve strength and endurance as well as combat stiffness and weakness associated with pain-related inactivity	Useful in regaining muscle and tendon strength, as well as improving ROM, endurance, comfort, and function Transforms painful activities into more easily tolerated ones Minimizes atrophy, demineralization, and deconditioning	Arthritis, LBP, fibromyalgia, CRPS
Gait and posture training	Appropriate attention to gait and posture, including preventive and therapeutic ergonomics	Relieve pain and restore function; prophylaxis against further pain	LBP, neck pain, tension HA
Applied heat or cold	Application of cold (cryotherapy) to decrease pain and swelling and improve function; later application of heat (thermotherapy) to augment performance and diminish pain	Application of cold produces local analgesia, slows nerve conduction, and promotes tendon flexibility Application of heat produces local analgesia, dilates (widens) blood vessels, and promotes flexibility	Acute trauma (e.g., injury, surgery); repetitive trauma, arthritis, muscle pain or spasm, acute LBP
Immobilization	Reduction of activity and avoidance of strain for certain duration; may involve brace to assist, restrict, or limit function of joint	May be needed to maintain proper alignment during post-injury repair but is generally harmful for patients with CNCP	Some postoperative, injury (e.g., fracture)
TENS	Selective stimulation of cutaneous receptors sensitive to mechanical stimuli (mechanoreceptors) by applying low-intensity current via skin electrodes[a]	TENS can reduce pain and analgesic use and improve physical mobility, presumably by interfering with transmission of nociceptive impulses in nerve fibers	Trauma, postoperative, labor, abdominal pain; neuralgias, other neuropathic pain, PVD, angina, musculoskeletal pain
PNS SCS IC	Electrical stimulation of selected regions of the nervous system via implantable devices[b]	The goal of electrical stimulation is to disrupt nociceptive signaling	Chronic pain of the trunk and limbs (e.g., PVD), neuropathic pain (deafferentation, poststroke pain), cancer pain
Massage	Rubbing of painful or nonpainful adjacent area	Facilitates relaxation and decreases muscle tension and pain	Postoperative pain, arthritis, fibromyalgia
Acupuncture	Old Chinese healing technique involves insertion of fine needles into the skin at varying depths; application of pressure at acupuncture sites is called acupressure	Acupuncture may cause the secretion of endorphins and interfere with transmission of nociceptive information to relieve pain	Postoperative, radiculopathy, chronic LBP, fibromyalgia

Sources: References 24, 72, 182, and 223-228.

[a]TENS appears to work best when applied to skin close to the pain's site of origin and when sense of touch and pressure are preserved.
[b]The implanted portion of the device consists of a pulse generator and leads connected to electrodes located in fascia in close proximity to a peripheral nerve (PNS), the spinal canal (SCS), or brain (IC). The patient or clinician controls stimulation using non-implanted system components.

CNCP: chronic noncancer pain; CRPS: chronic regional pain syndrome types I and II; HA: headache; IC: intracerebral stimulation; LBP: lower back pain; PNS: peripheral nerve stimulation; PVD: peripheral vascular disease; ROM: range of motion; SCS: spinal cord stimulation; TENS: transcutaneous electrical nerve stimulation.

Section IV:

Management of Acute Pain and Chronic Noncancer Pain

A. Acute Pain

This section reviews the general approach to the treatment of acute pain, including treatment goals, therapeutic strategies, and elements of pain management. It also provides an overview (i.e., summary tables) of the treatment of some common types of acute pain.

1. Treatment Goals

As addressed in Section I.C.1, acute pain is a complex multidimensional experience that usually occurs in response to tissue trauma. Whereas responses to acute pain may be adaptive, they can have adverse physiologic and psychological consequences (e.g., reduced tidal volume, excessive stress response, progression to chronic pain, inability to comply with rehabilitation, patient suffering and dissatisfaction). Acute pain is more difficult to manage if permitted to become severe,[1] so prompt and adequate treatment of acute pain is imperative. Treatment goals and strategies for acute pain can be summarized as:

- Early intervention, with prompt adjustments in the regimen for inadequately controlled pain
- Reduction of pain to acceptable levels
- Facilitation of recovery from underlying disease or injury.

2. Therapeutic Strategies

a. Multimodal analgesia

Recent research on postoperative pain management supports a treatment approach known as "multimodal analgesia" or "balanced analgesia." This approach involves the use of more than one method or modality of controlling pain (e.g., drugs from two or more classes, drug plus nondrug treatment) to obtain additive beneficial effects, reduce side effects, or both.[2] These modalities may operate through different mechanisms or at different sites (i.e., peripheral versus central actions). One example of multimodal analgesia is the use of various combinations of opioids and local anesthetics to manage postoperative pain.[3-5] Table 32 summarizes some specific examples of multimodal therapy.

Table 32. Examples of Multimodal Therapy

Combination of Agents	Example
Systemic NSAID[a] plus systemic opioid	PO Ibuprofen plus PO hydromorphone
Systemic NSAID plus epidural opioid and local anesthetic	IV ketorolac plus epidural fentanyl and bupivacaine
Systemic NSAID plus local infiltration of anesthetic plus systemic opioid	IV ketorolac plus lidocaine infiltration of surgical site plus IV PCA morphine
Regional block plus systemic NSAID plus epidural opioid and local anesthetic	Intraoperative anesthetic plus IV ketorolac plus postoperative fentanyl and bupivacaine epidural

Source: Reference 6.

[a]NSAIDs need to be used with care in surgical patients due to the risk of bleeding ("anti-platelet" effect).

IV: intravenous; NSAID: nonsteroidal anti-inflammatory drugs; PCA: patient-controlled analgesia; PO: per os (oral).

Benefits of multimodal analgesia include earlier oral intake, ambulation, and hospital discharge for postoperative patients as well as higher levels of participation in activities necessary for recovery (e.g., physical therapy).[6-7] It also may reduce postoperative morbidity, mortality, and costs.[8] Some pain experts advocate revision of traditional postoperative care programs to include accelerated multimodal postoperative recovery programs.[9] Additional potential applications of multimodal analgesia include other types of acute, as well as chronic, pain.[2]

b. Preemptive analgesia

Preemptive analgesia refers to the administration of one or more analgesic(s) prior to a noxious event (e.g., surgery) in an attempt to prevent peripheral and central sensitization, minimizing post-injury pain (see I.B.7,8). Compelling evidence of the efficacy of preemptive analgesia exists in animal models, and human studies have produced some promising results. For example, the preoperative administration of selective cyclooxygenase-2 (COX-2) inhibitors decreased use of morphine after spinal fusion surgery in one recent study.[10] There is also some evidence that preoperative epidural blockade (local anesthetic and opioid with or without clonidine) may reduce the incidence of phantom limb pain in patients undergoing limb amputation.[11-12]

However, other studies have failed to confirm that preemptive analgesia prevents phantom

limb pain.[a,13-14] Furthermore, a recent review of 40 controlled clinical studies revealed no difference in the intensity and duration of postoperative pain after preemptive analgesia with a variety of drugs.[15] This failure to demonstrate clinical efficacy may reflect failure to identify the optimum method or timing for instituting the analgesia. Some investigators contend that multiple factors (e.g., extent and nature of the damaged tissue, duration of the surgery, choice of drug, route and timing of administration, time course of central sensitization) may influence the ability to demonstrate a preemptive analgesic effect.[16] Thus, clinical research into its potential clinical benefits is continuing.

3. Elements of Treatment

a. Pharmacologic management

Pharmacologic management is the cornerstone of acute pain management. Multiple factors (e.g., pain intensity, quality, and pattern; patient preferences; drug side effect profiles) influence the selection of medications. Most acute pain is nociceptive and responds to nonopioids and opioids. However, some adjuvant analgesics (e.g., local anesthetics) also are used to manage acute pain.

In general, mild somatic pain responds well to oral nonopioids (e.g., acetaminophen, nonsteriodal anti-inflammatory drugs [NSAIDs]), topical agents (e.g., local anesthetics), and physical treatments (e.g., rest, ice, compression, elevation).[1] Moderate to moderately severe acute pain is more likely to require opioids.[17-18] Nonopioids often are combined with opioids to improve pain relief and diminish the risk of side effects. Various factors (e.g., preferred route of administration, time of onset, dosing frequency, side effect profile) influence the choice of individual agents in a drug class.

Excessive concern about addiction and regulatory scrutiny heavily contribute to the undertreatment of pain (see I.E.4,5). Analgesics, especially opioids, are underprescribed and underdosed for both acute and chronic pain. Moderate to severe acute pain should be treated with sufficient doses of opioids to safely relieve the pain. If drug side effects preclude achieving adequate pain relief, the side effects should be treated and/or another opioid should be tried. The concomitant use of other analgesics (e.g., nonopioids, local anesthetics) and nonpharmacologic methods (e.g., applied heat or cold, electroanalgesia, relaxation) maximizes pain relief and minimizes the risk of treatment-limiting side effects.

b. Nonpharmacologic approaches

Nonpharmacologic approaches to acute pain management should supplement, but not replace, analgesics.[1] However, the medical condition of some patients with acute pain (e.g., severe trauma or burns) may limit the use of nonpharmacologic therapy. Postoperative patients who receive preoperative instruction in simple psychological methods (Table 30) such as relaxation and imagery are especially likely to benefit. Thus, instruction in nonpharmacologic methods of pain management is an important part of the preoperative assessment (Table 12). Physical methods of pain management can be helpful in all phases of care, including immediately after tissue trauma (e.g., rest, application of cold, compression, elevation) and late during the healing period (e.g., exercises to regain strength and range of motion) (Table 31).

4. Management of Some Common Types of Acute Pain

Table 33 defines and presents examples of some common types of acute pain, including pain associated with an acute illness, perioperative pain, posttraumatic pain (major and minor), procedural pain, and obstetrical pain. Tables 34 to 36 summarize some pharmacologic and nonpharmacologic approaches to the management of these types of pain. The former category is divided into medications administered via systemic routes (Table 34) and those administered regionally (i.e., regional anesthesia)(Table 35). The reasons these pain types were selected for discussion include:

- Their relatively high prevalence
- The availability of effective pharmacologic and nonpharmacologic methods of management
- The availability of clinical practice guidelines

[a] Nikolajsen and colleagues[13] found that the rate and intensity of phantom and stump pain, as well as the consumption of opioids, did not differ significantly between 29 patients randomly assigned to receive epidural bupivacaine and morphine before, during, and for 1 week after the lower-limb amputation and 31 control-group patients who received epidural saline before and during the amputation then oral or intramuscular morphine. Lambert et al.[14] reported that a perioperative epidural block started 24 hours prior to amputation was not superior to the intra- and post-operative infusion of a local anesthetic via a perineural catheter in preventing phantom pain. However, the former did provide better relief of stump pain during the immediate postoperative period.

Table 33. Common Types of Acute Pain

Type or Source	Definition	Source or Examples
Acute illness	Pain associated with an acute illness	Appendicitis, renal colic, myocardial infarction
Perioperative (includes postoperative)[a]	Pain in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or both	• Head and neck surgery • Chest and chest wall surgery • Abdominal surgery • Orthopedic and vascular surgery (back, extremities)
Posttraumatic (major trauma)	Includes generalized or regionalized pain due to a major acute injury	Motor vehicle accident
Posttraumatic (minor trauma)	Pain due to a minor acute injury	Sprain, laceration
Burns	Pain due to thermal or chemical burns	Fire, chemical exposure
Procedural	Pain associated with a diagnostic or therapeutic medical procedure	Bone marrow biopsy, endoscopy, catheter placement, circumcision, chest tube placement, immunization, suturing
Obstetrical	Pain related to labor and delivery	Childbirth by vaginal delivery or Cesarean section

Sources: References 1 and 19.

[a]The American Society of Anesthesiologists defines acute pain in the perioperative setting as "pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources."[19] Thus, perioperative pain includes postoperative pain (i.e., pain that follows surgery).

(CPGs) outlining appropriate care
- Evidence of undertreatment and/or nonadherence to relevant CPGs.

These tables merely provide an overview of treatments. They do not consider all of the risks associated with treatments or the needs of special populations. The reader should refer to the appropriate CPGs to make specific management decisions.

B. Chronic Noncancer Pain

This section reviews general approaches to the treatment of chronic noncancer pain (CNCP), including treatment goals, therapeutic approaches, and elements of treatment. It also provides general information about the treatment of some common types of CNCP (i.e., summary tables) and identifies relevant clinical practice guidelines (CPGs).

1. Treatment Goals

As discussed in Section I.C.4, CNCP is a debilitating condition that often is associated with significant physical, emotional, and social disability. A complex interaction among these factors contributes to the persistence of pain. Therefore, treatment should address important social and psychological consequences of the pain as well as any physical pathology. Usually this entails a comprehensive approach that includes medication and functional rehabilitation.[28]

Functional rehabilitation helps the patient develop skills to manage the pain. It includes patient education, regular assessment, management of contributing illnesses (e.g., depression), and the setting of attainable treatment goals.[28] The latter should take into account factors such as the patient's acceptance of his or her condition, the patient's motivation to participate in treatment, the patient's ability to follow through with recommendations, and the available time and resources.[29] General treatment goals for CNCP include:[2,28-30]

- Diminish suffering, including pain and associated emotional distress
- Increase/restore physical, social, vocational, and recreational function
- Optimize health, including psychological well-being
- Improve coping ability (e.g., develop self-help strategies, reduce dependence on health care system) and relationships with others (e.g., family, friends, health care professionals).

Table 34. Systemic Medications for Acute Pain Management

Pain Type or Source	Nonopioids	Opioids	Adjuvant Analgesics	Other	Comments
Acute illness	Acetaminophen, NSAIDs	Systemic opioids			
Perioperative pain[a]	Acetaminophen, NSAIDs[b]	Systemic opioids[c], including PCA[d]	Local anesthetics (e.g., idocaine, bupivacaine[e])		Use multimodal therapy when possible Recognize needs of special populations Scheduled ATC dosing generally preferred to PRN
Major trauma (generalized pain)	Acetaminophen, NSAIDs during post-trauma healing phase	Bolus or continuous IV opioids[f] during emergency phase; PO or IV opioids during healing phase	IV ketamine (very rare)	Inhaled NO	Use of ketamine is restricted to pain refractory to other treatments due to severe CNS side effects Inhaled NO is used for incident pain
Major trauma (regionalized pain)	NSAIDs (parenteral, oral) during post-trauma healing phase	Bolus or continuous IV opioids during emergency phase plus regional anesthesia	IV ketamine (very rare)	Inhaled NO	Use of ketamine is restricted to pain refractory to other treatments due to severe CNS side effects Inhaled NO is used for incident pain
Burns	Acetaminophen, NSAIDs during rehabilitative phase (i.e., no early role)	High doses of IV opioids (e.g., morphine, fentanyl) ± PCA for NPO patients; oral opioids (e.g., morphine, hydromorphone) when taking PO	Parenteral ketamine (very rare) IV lidocaine (very rare)	BNZ Inhaled NO	Use of ketamine is restricted to pain refractory to other treatments due to severe CNS side effects Inhaled NO is used for incident pain Infusion of low-dose lidocaine is restricted to burn pain refractory to opioids Lorazepam or midazolam for background and procedural anxiolysis
Minor trauma	Acetaminophen, NSAIDs	Opioids for mild-to-moderate pain			
Procedural pain	NSAIDs for preemptive analgesia and post-procedural pain	IV opioids (e.g., morphine, hydromorphone, fentanyl) unless contraindicated[g]	Local anesthetics (e.g., EMLA®, lidocaine, bupivacaine, ropivacaine) IV ketamine	BNZ (e.g., diazepam, lorazepam, midazolam) Inhaled NO Propofol[h]	Local anesthetics may be applied topically (e.g., EMLA®), injected into tissue, or used for nerve blocks Use of ketamine limited by severe CNS side effects
Obstetrical pain		Bolus IV opioids (e.g., fentanyl, hydromorphone, morphine)			

Sources: References 1 and 17-24.

[a]The American Society of Anesthesiologists defines acute pain in the perioperative setting as pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources.[19] Thus, perioperative pain includes postoperative pain (i.e., pain that follows surgery).
[b]Unless contraindicated, NSAIDs (and acetaminophen) are recommended for mild-to-moderate postoperative pain, and parenteral ketorolac may be used for moderate-to-severe pain.[1] Continue nonopioids even after adding opioids for opioid-sparing effects.[1]
[c]Moderately severe to severe postoperative pain should initially be treated with an opioid analgesic with or without an NSAID.[1] Morphine is the standard agent for opioid therapy; if contraindicated, hydromorphone may be substituted.[1]
[d]Preferred route of administration is IV (bolus or continuous PCA). Rectal and subcutaneous are alternative routes of administration. Switch to oral administration when the patient can take medication by mouth.
[e]Local anesthetics may be combined with opioids for intraspinal analgesia or used for regional nerve blocks.
[f]Titrate opioids carefully to maintain stable cardiovascular and respiratory status. Monitor neurological and neurovascular status continuously in patients with head injury or limb injury, respectively.[1]
[g]Contraindications to opioid analgesia include altered sensorium, full-term pregnancy, lung disease, or inability to monitor and manage certain side effects (e.g., respiratory depression).[1]
[h]Hypnotic general anesthetic that produces good sedation.

ATC: around-the-clock; BNZ: benzodiazepines; CNS: central nervous system; EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); IV: intravenous; LAs: local anesthetics; NO: nitrous oxide; NPO: nothing per os (by mouth); NSAIDs: nonsteroidal anti-inflammatory drugs, including aspirin: PO: per os (oral); PCA: patient-controlled analgesia; PRN: as needed; TD: transdermal.

Table 35. Regional Anesthesia for Acute Pain Management

Perioperative pain[a]	• Epidural anesthesia with opioids or opioid plus local anesthesia mixture injected intermittently or infused continuously[b] • Intrathecal opioids or opioid plus local anesthetics • Local neural blockade[c] • Other regional anesthesia[d] techniques
Trauma	• Limited to local neural blockade[c] during emergency phase • Also includes epidural analgesia with opioids and/or local anesthetics during post-trauma healing phase, especially for regionalized pain[e]
Burns	• Epidural analgesia with opioids and/or local anesthetics (only after closure of burn wound)
Procedural	• Includes local infiltration with local anesthetics
Obstetrical pain[f]	• Epidural analgesia[g] or spinal analgesia with local anesthetics (e.g., bupivacaine, ropivacaine) and/or opioid • Combined spinal-epidural techniques (combined spinal-epidural techniques)[h] with opioids • Epidural analgesia, spinal, or combined spinal-epidural techniques for Cesarean section • Tissue infiltration with local anesthetics

Sources: References 1, 19-20, and 22-24.
[a]The American Society of Anesthesiologists defines acute pain in the perioperative setting as "pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources."[19] Thus, perioperative pain includes postoperative pain (i.e., pain that follows surgery).
[b]Good analgesia but risk of delayed-onset respiratory depression; requires careful monitoring for potential complications (e.g., abscess development, anesthesia of a nerve root at the site of catheter tip).[1] Addition of a local anesthetic has opioid-sparing effect and improves analgesia.
[c]Local neural blockade is by intermittent (e.g., intercostal nerve blockade with local anesthetics or cryoprobe) or continuous (infusion of local anesthetic through an interpleural catheter) methods.
[d]Other regional anesthesia techniques include: infiltration of incisions with local anesthetic.
[e]Useful when not contraindicated by sepsis, coagulopathy, or cardiorespiratory instability.[1] Must clear spine before using central conduction block or intraspinal opioids.[23]
[f]Goal of regional anesthesia in pregnant women is to provide adequate analgesia with as little block as possible.[20]
[g]Epidural anesthesia is preferred to spinal analgesia and parenteral opioids due to superior analgesia and decreased risk of maternal and/or fetal complications.[20] Epidural analgesia with opioids with a local anesthetic provides better analgesia than epidural anesthesia with local anesthetics alone but is associated with greater risk of complications.[20]
[h]Combined spinal-epidural techniques may provide rapid and effective analgesia for labor, but there is a higher risk of side effects.[20]

Table 36. Nonpharmacologic Interventions for Acute Pain

Pain Type or Source	Physical Methods[a]	Psychological Methods	Other
Acute illness	• Vibration or cold for some HA; immobilization	Patient education, relaxation, imagery, distraction	
Perioperative pain[b]	• Exercise or immobilization • Massage • Application of heat or cold • Electroanalgesia (e.g., TENS)	Patient education, relaxation, distraction, imagery, biofeedback, hypnosis	Acupuncture
Trauma	• Rest, ice, compression, elevation (RICE) • Physical therapy (e.g., stretching, strengthening, thermal therapy, TENS, vibration)	Relaxation, hypnosis, distraction, supportive psychotherapy, coping skills training	
Burns	• Limb elevation • Minimize number of dressing changes	Patient education, distraction, deep relaxation, imagery, hypnosis, operant conditioning	
Procedural	• Application of cold (pre- and post-procedure) • Counterirritation methods (e.g., simple massage, scratching, pressure) • Rest or immobilization (post-procedure)	Patient education, relaxation, distraction, imagery, music relaxation	
Obstetric		Patient education, relaxation breathing, distraction	

Sources: References 1, 18-19, and 21-27.
[a]Physical agents or modalities provide pain relief, improve physical function, and reduce fears associated with pain-related immobility or activity restriction.[1]
[b]The American Society of Anesthesiologists defines acute pain in the perioperative setting as "pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources."[19] Thus, perioperative pain includes postoperative pain (i.e., pain that follows surgery).
HA: headache; TENS: transcutaneous electrical nerve stimulation.

2. Therapeutic Strategies

a. Multimodal therapy

As with acute pain, the literature and various CPGs support the use of multimodal therapy for chronic pain. In their 1997 Practice Guidelines for Chronic Pain Management, the American Society of Anesthesiologists (ASA) defines multimodal therapy as the "concomitant use of separate therapeutic interventions under the direction of a single practitioner to obtain additive beneficial effects or reduction of adverse effects."[2]

Examples of multimodal therapy include use of:

- Medications from different classes (i.e., combination drug therapy)
- Rehabilitative therapies (e.g., physical therapy, occupational therapy) and medications
- Regional anesthesia (e.g., neural blockade) and medications.

b. Interdisciplinary approach to rehabilitation

The literature[31-32] and various organizations (e.g., the Commission on Accreditation of Rehabilitation Facilities [CARF], the American Academy of Family Physicians [AAFP]) also support the use of an interdisciplinary rehabilitative approach to the management of chronic pain. This refers to a process in which health care professionals with disparate training collaborate to diagnose and treat patients suffering from difficult pain states. The Rehabilitation Accreditation Commission (also known as CARF) defines a chronic pain management program (CPMP) as [one that] "provides coordinated, goal-oriented, interdisciplinary team services to reduce pain, improve functioning, and decrease the dependence on the health care system of persons with chronic pain syndrome."[33-34] Various reviews of program outcomes suggest that potential benefits of participation in a CPMP include reduced pain intensity, improved sense of control over the pain, physical reconditioning, lower use of opioids and health care resources, reduced health care costs, and increased employment.[2,30-32,35-36]

Essential functions of a CPMP include medical diagnosis, assessment of physical function, psychosocial assessment, pharmacologic therapy, physical rehabilitation, patient education, and appropriate psychological approaches (e.g., relaxation, biofeedback, coping skills training, psychotherapy).[30,36] In some patients, more invasive approaches (e.g., nerve blocks, trigger point or steroid injections, epidural or intrathecal analgesia, neurosurgical procedures) and/or intensive chronic pain rehabilitation are warranted. Team members represent a number of health care disciplines and include physicians (e.g., neurologists, psychiatrists, anesthesiologists, rheumatologists, neurosurgeons, physiatrists), nurses, pharmacists, case managers, social workers, physical therapists, occupational therapists, and vocational counselors.[37] Interventions are diverse, as summarized in Table 37.

Table 37. Interdisciplinary Management of CNCP: Examples of Interventions

- Patient education: counseling about the pain, aggravating and alleviating factors, management strategies, lifestyle factors that may influence the pain (e.g., use of nicotine, alcohol.
- Physical rehabilitative approaches: physical therapy modalities for reconditioning (e.g., walking, stretching, exercises to improve strength and endurance, oscillatory movements)
- Other physical approaches: application of heat or cold, TENS, massage, acupuncture
- Occupational therapy: attention to proper body mechanics, resumption of normal levels of activities of daily living
- Pharmaceuticals: nonopioids, opioids, antidepressants, antiepileptic drugs, stimulants, antihistamines
- Regional anesthesia: nerve blocks (e.g., diagnostic, somatic, sympathetic, visceral, trigger point) and/or intraspinal analgesia (e.g., opioids, clonidine, baclofen, local anesthetics)
- Psychological approaches: relaxation training, hypnosis, biofeedback, copings skills, behavior modification, psychotherapy
- Surgery: neuroablation, neurolysis, microvascular decompression

Sources: References 2, 28, 30, and 36-37.

CNCP: chronic noncancer pain; TENS: transcutaneous electrical nerve stimulation.

3. Elements of Treatment

a. Pharmacologic management

Although similarities exist, the pharmacologic management of CNCP differs from that for acute pain in some important ways.

Greater use of adjuvant analgesics: The greater use of adjuvant analgesics for chronic pain reflects, in part, the greater frequency of neuropathic pain and reduced responsiveness of such pain to traditional analgesics. The results of multiple placebo-controlled clinical trials and various CPGs[2,28] support the use of antidepres-

sants, antiepileptic drugs, and local anesthetics as first-line approaches to the treatment of chronic pain. The 1997 ASA CPGs for Chronic Pain Management state that membrane stabilizing agents, antidepressants, and NSAIDs "provide analgesic and health benefits" in patients with chronic pain.[2] The 2000 AAFP CPGs for the treatment of CNCP note that secondary benefits of antidepressants include improved sleep and the treatment of any associated depression or anxiety.[28] Similarly, the antiepileptic drug gabapentin improves sleep and mood, as well as pain and quality of life, in patients with some types of neuropathic pain.[38-39]

More judicious use of opioids: For many years, use of opioids to treat CNCP was considered ill-advised. This position reflected multiple fears and concerns, including the potential for iatrogenic addition, declining efficacy, toxicities, and potential interference with optimal functioning (e.g., promotion of regression, reinforcement of pain behaviors, diversions, decreased motor and cognitive functioning).[40] However, a number of pain-related organizations and experts have expressed recent support for the judicious use of opioids in patients with chronic pain. For example, the American Academy of Pain Medicine and the American Pain Society recently issued a statement that supports the use of opioids in select patients with CNCP.[41] As with other medical interventions, such a decision must be based on careful consideration of the ratio of benefits to risks (e.g., toxicity, functional impairment, addiction).[b,40] Table 38 summarizes some recommendations regarding use of opioids in patients with CNCP.[48]

b. *Nonpharmacologic approaches*

Nonpharmacologic approaches play a key role in managing CNCP. Patient education is potentially the most critical therapy, as it is often essential for rehabilitation. Invalidism and family enabling may result from uncertainty or inaccurate information.[30] Reconditioning reduces pain, promotes physical and psychological rehabilitation, and empowers the patient. In addition to reducing emotional distress, psychological techniques (e.g., relaxation, biofeedback) can relax muscles and reduce autonomic nervous arousal. In its 2000 CPGs, the AAFP recommends the use of nonpharmacologic interventions (i.e., patient education, physical therapy [PT], occupational therapy [OT], treatment of coexisting psychological disorders) in the management of all patients with CNCP.[28]

Table 38. Recommendations for Opioid Therapy in Patients with Chronic Noncancer Pain

Before treatment:

- Perform comprehensive assessment, including a pain history and assessment of the impact of the pain, a directed physical examination, a review of prior diagnostic study results or interventions, a drug history (i.e., past abuse), and an assessment of coexisting diseases or conditions.
- Consider obtaining a second opinion from a physician or psychologist with expertise in pain management and use of interdisciplinary team.
- Optimize nonpharmacologic and nonopioid therapies.
- Inform patient of potential risks of use of controlled substances, including addiction (informed consent)
- Agree on issues including how drugs will be provided, acceptable number of rescue doses, pharmacy to be used for prescription refills, and the follow-up interval.

During treatment:

- Administer opioids primarily via oral or transdermal routes, using long-acting medications when possible
- Use a fixed dosed ("around-the-clock") regimen.
- Perform careful drug titration, balancing analgesia against side effects.
- Continue efforts to improve analgesia via complementary approaches (e.g., behavioral approaches, formal rehabilitation program, other medications).
- Consider use of hospitalization for pain that is not treated by transient, small dose increments.
- Monitor for evidence of drug hoarding, unauthorized dose increases, and other aberrant behavior. Reconsider therapy in the occurrence of such behaviors.
- Perform frequent follow-up evaluation to monitor analgesia, side effects, functional status, quality of life, and any evidence of medication misuse.
- Consider use of self-report instruments (e.g., pain diary).
- Carefully document the overall pain management treatment plan and include the reason for opioid prescribing, any consultations received, and results of periodic review of the patient's status.

Sources: References 29, 41, and 48.

4. Management of Some Common Types of Chronic Noncancer Pain

There are many types of CNCP. This section provides a brief overview through the summary tables of a few common types. In addition to their relatively high prevalence, these pain types were selected because effective treatments and/or evidence of inadequate management

[b] Some studies have shown beneficial effects of long-term opioid therapy in carefully selected patients with CNCP, including reduced pain, improved performance, and enhanced quality of life.[42-44] However, clinicians should remain aware of the potential for opioid-induced hyperalgesia and/or analgesia without associated improvement in function in some patients.[40,43,45-47]

exist. Tables 39 to 42 summarize management approaches, including systemic administration of medications (Tables 39 and 40), interventional techniques (Table 41), and nonpharmacologic strategies (Table 42), for the following types of CNCP:

Arthritis pain

Arthritis pain can result from more than 100 rheumatic diseases, which cause pain, stiffness, and swelling of joints as well as damage to supporting structures.[55] Osteoarthritis (OA) and rheumatoid arthritis (RA) are the most common types of arthritis. OA (often referred to as degenerative joint disease) is characterized by a progressive loss of articular (joint) cartilage, mostly affecting weight-bearing and frequently used joints (e.g., hip, knee).[53] It often manifests as deep aching pain, stiffness, and limited range of motion. RA is a common inflammatory arthritis of unknown etiology that affects multiple joints.[53] RA manifests clinically as aching,

Table 39. Pharmacologic Management for Chronic Noncancer Pain: Selected Examples

Type of Pain	Nonopioids	Opioids	Adjuvant Analgesics and Disease-Specific Drugs	Comments
Arthritis pain	Acetaminophen NSAIDs Selective COX-2 inhibitors[a]	Short-term, mild opioids for flare-ups	Corticosteroids (oral for RA, injections for OA and RA) Topical capsaicin DMARDs[b] (e.g., MTX, DP, gold salts, AZA, SSZ, HCQ) BRM[c] (e.g., entanercept, inflixmab)	Select NSAID based on dosing, efficacy, tolerance, costs, and patient preference Monitor closely for NSAID side effects Selective COX-2 inhibitors have a lower incidence of certain side effects Opiods are appropriate for long-term treatment in selected patients
Low back pain	Acetaminophen NSAIDs Selective COX-2 inhibitors	Short-term opioids for mild-to-moderate flare-ups	TCAs (e.g., amitriptyline, nortriptyline) AEDs Muscle relaxants (short term)	Opioids are appropriate for long-term treatment in selected patients
Fibromyalgia	Acetaminophen NSAIDs Selective COX-2 inhibitors	Opioids (occasional use for "flares") Tramadol	TCAs (e.g., amitriptyline, nortriptyline, doxepin) Muscle relaxants (short- term) (e.g., cyclobenzaprine)	Tramadol may have less potential for abuse
Sickle cell disease pain	Acetaminophen, NSAIDs	Short-acting[d] or long-acting opioids	Sedatives Anxiolytics	Use short-acting opioids for short-term treatment and longer-acting opioids for longer treatment
Peripheral neuropathy (e.g., PDN, PHN)	Acetaminophen NSAIDs	Opioids (short-term only)	TCAs (e.g., amitriptyline) AEDs (e.g., gabapentin, carbamazepine, valproate) Topical agents (e.g., lidocaine patch, capsaicin) Local anesthetics (e.g., lidocaine, mexiletine)[e] (rarely used) NMDA antagonists (e.g., ketamine[f]) (rarely used)	AEDs, TCAs, and topical local anesthetics are first-line treatments Lidoderm® is first FDA-approved treatment for PHN Placebo-controlled trials found TCAs and gabapentin equally effective for treatment of PDN and PHN NSAIDs are rarely effective Try opioids as last resort

Sources: References 17, 38-39, and 49-70.

[a]Initial recommended treatment for OA includes acetaminophen and nonpharmacologic management (e.g., education, exercises, joint protection).[49-51] Patients who need additional pain relief and symptom control should receive low- or full-dose NSAIDs, topical capsaicin, or corticosteroids, as indicated. The initial drug treatment of RA usually involves NSAIDs.[52] Patients with inadequate response to NSAIDs may require DMARDs.[52]

[b]DMARDs are associated with multiple toxicities; therefore, they require careful balancing of the risks and benefits and close patient monitoring.[52]

[c]Biological response modifiers are used to reduce symptoms in some patients with RA.[53]

[d]Morphine or hydromorphone is preferred to meperidine due to potential toxicity of the meperidine metabolite.[54]

[e]These medications are contraindicated in patients with cardiac conduction abnormalities, left ventricular dysfunction, or severe liver or renal disease. Topical lidocaine (Lidoderm®) is not associated with the toxicities seen with systemic administration of lidocaine.

[f]NMDA antagonists are effective but are used very rarely due to severe central nervous system side effects.

AEDs: antiepileptic drugs; AZA: azathioprine; BRM: biological response modifiers; COX-2 inhibitors: cyclooxygenase-2 inhibitors; DMARDs: disease-modifying anti-rheumatic drugs; DP: D-penicillamine; FDA: Food and Drug Administration; HCQ: hydroxychloroquine; MTX: methotrexate; NMDA: N-methyl-D-aspartate; NSAIDs: nonsteroidal anti-inflammatory drugs; OA: osteoarthritis; PDN: painful diabetic neuropathy; PHN: postherpetic neuralgia; RA: rheumatoid arthritis; SSZ: sulfasalazine; TCAs: tricyclic antidepressants.

burning joint pain (often with swelling and redness), joint enlargement, joint and muscle stiffness, and various constitutional symptoms (e.g., fatigue, weakness, fever, weight loss). OA affects about 16 million, mostly older, Americans, whereas approximately 2.1 million Americans suffer from RA.[55] Approaches to management of arthritis pain include medications (e.g., disease-modifying anti-rheumatic drugs, nonsteriodal anti-inflammatory drugs, acetaminophen), physical rehabilitative approaches (e.g., exercises, OT, PT, massage, heat and cold, electroanalgesia), psychological approaches, and in some cases, acupuncture or surgery (Tables 39, 41, and 42).[49-52,55, 90]

b. Chronic low back pain

Chronic low back pain (LBP) is the commonest cause of disability in industrialized nations. About four out of five Americans will experience back pain at some point in their lives.[86] Whereas (acute) back pain resolves within 4-6 weeks in 90% of patients,[59-60] the pain persists in others. LBP has many causes (e.g., trauma, musculoskeletal spasm, arthritis, herniated disc with nerve compression, myofascial pain, ankylosing spondylitis, spinal stenosis, arachnoiditis, cancer, kidney disease, obesity) but, in most cases, no specific cause can be identified.[59-60] Management options for chronic LBP include medications, psychological approaches (education, "back school," psychotherapy, biofeedback), exercises, other physical approaches (e.g., OT, PT, electroanalgesia, heat and cold) and, in some cases, acupuncture, manipulation, or surgery (Tables 39, 41, and 42).[28,58,60-61]

c. Fibromyalgia

Fibromyalgia is a chronic syndrome that manifests as widespread musculoskeletal pain and multiple "tender points" localized to areas in the neck, spine, shoulders, and hips.[64] In addition to chronic pain with acute flares, patients often experience sleep disturbances, morning stiffness, anxiety, and irritability.[63-64] Fibromyalgia is diagnosed based on criteria established by the American College of Rheumatology.[64] Its cause is unknown, but theories about its etiology include trauma and infection.[63] About 3 to 6 million Americans suffer from fibromyalgia,

Table 40. Pharmacologic Management of Migraine and Other Types of Headache

Headache Type	Prophylaxis	Abortive	Comments
Migraine	AEDs (e.g., divalproex sodium[a], gabapentin) BBs (e.g., propranolol, timolol)[a] CCBs (e.g., verapamil, nimodipine) TCAs (e.g., amitriptyline) NSAIDs (e.g., ASA, flurbiprofen) Estradiol[b] Methysergide[c]	NSAIDs (e.g., ASA, ibuprofen, naproxen, diclofenac, flurbiprofen, piroxicam) Opioids, including butorphanol[d] Combination treatment: • Acetaminophen plus ASA plus caffeine • ASA plus butalbital plus caffeine[e] • Acetaminophen plus codeine Dihydroergotamine[f]: (intranasal, SC, IV) Selective $5HT_{1B/1D}$ receptor agonists ("tripans") • Rizatriptan (PO) • Zolmitriptan (PO) • Sumatriptan (PO, SC, or intranasal)	Acetaminophen plus ASA plus caffeine considered first-line treatment First-choice NSAIDs are ASA, ibuprofen, and naproxen; others also are effective Triptans are effective and appropriate initial choice for patient with mild to severe HA and no contraindications
Tension	TCAs (e.g., amitriptyline, doxepin)	Acetaminophen NSAIDs	
Cluster	CCBs (e.g., verapamil) Corticosteroids Methysergide AEDs (e.g., divalproex sodium)	Ergotamine Dihydroergotamine Inhalation of oxygen	

Sources: References 71-80.

[a]Divalproex sodium, timolol, and propranolol are indicated for migraine prophylaxis.

[b]Estradiol administered premenstrually can prevent migraine in women who have migraine related to menses.[71-74]

[c]Methysergide is effective but of limited utility due to the risk of complications (e.g., retroperitoneal or retropleural fibrosis).[71-74]

[d]Intranasal butorphanol is effective for migraine[71-74] and is good rescue therapy.[75] IV opioids also may be appropriate for rescue therapy.[71-74]

[e]This combination requires careful monitoring due to the potential for abuse of butalbital.[71-74]

[f]Consider dihydroergotamine for headaches that have not responded to other first-line treatments or patients who cannot take PO.

5-HT: 5-hydroxytryptamine; AEDs: antiepileptic drugs; ASA: aspirin; BBs: beta blockers; CCBs: calcium channel blockers; HA: headache; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; PO: per os (oral); SC: subcutaneous; TCAs: tricyclic antidepressants.

Table 41. Regional Anesthesia for Chronic Noncancer Pain

Pain Type	Method
Arthritis pain	Intra-articular injection[a] of corticosteroids (e.g., methylprednisolone) Intra-articular injections of sodium hyaluronate[b]
Low back pain	Facet joint injections with local anesthetic[c] Sciatic nerve block with local anesthetic for backache due to sciatica Epidural steroid injections (e.g., methylprednisolone), often with local anesthetic (e.g., lidocaine)[d]
Headache and migraine	Occipital nerve block with local anesthetic for occipital headache

Sources: References 51 and 83-84.

[a]Corticosteroid injections are used for the knees and hips and are limited to 3-4 per year.[51]

[b]These injections are approved for the knee, and studies have shown mixed results in regard to efficacy.[81-82]

[c]Controversy exists over the efficacy of therapeutic facet blocks but they are useful diagnostic blocks.[83]

[d]Controversy exists over the efficacy of epidural steroids for low back pain. Frequent epidural steroids can suppress hypothalamic-pituitary-adrenal axis function. Also, there is the potential for complications due to the epidural approach (e.g., hematoma, infection), the steroids (e.g., hypertension, hyperglycemia), or local anesthetic (heart arrhythmias).[84]

mostly women of child-bearing age.[64] Fibromyalgia generally is managed with medications, psychological approaches (education, relaxation therapy, hypnosis, psychotherapy), aerobic exercise, other physical approaches (e.g., OT, PT, electroanalgesia, heat and cold, vibration), and in some cases, acupuncture or manipulation (Tables 39 and 42).[56,63,91]

d. Sickle cell disease pain

Sickle cell disease (SCD) refers to a group of inherited blood disorders in which an abnormal form of hemoglobin, hemoglobin S, is the predominant form of hemoglobin. Chronic hemolytic anemia and vaso-occlusive events are its major pathologic features, and the primary clinical manifestation of SCD is pain.[54] Deoxygenated hemoglobin S causes red blood cells to sickle (change shape) at sites of low oxygen availability, stick to the lining of small blood vessels, and occlude (plug) them. Along with inflammation, these vaso-occlusive events cause pain. Other causes of pain in these patients include infection, infarction, and the accumulation of blood in various organs. According to the 1999 American Pain Society G*uideline for the Management of Acute and Chronic Pain in Sickle Cell Disease*, SCD pain may be acute, chronic, or of mixed duration and attributable to the disease or its treatment.[54] Sickle cell pain is managed with medications, physical approaches (e.g., adequate hydration, applied heat, PT, massage, ultrasound, electroanalgesia) and psychological approaches (e.g., deep breathing, relaxation, biofeedback) appropriate for acute and chronic pain management (Tables 39 and 42).[54,66] SCD is also managed with a various treatments (e.g., transfusions) that reduce sickling.

e. Peripheral neuropathy

Peripheral neuropathy (PN) is a disorder caused by damage to one or more peripheral nerve(s). Its incidence is unknown, but it is a common feature of many systemic diseases.[89] Diabetes and alcohol are the most common causes of PN in developed countries.[89] Other causes include other endocrine disorders and nutritional deficiencies, infection (e.g., post herpetic neuralgia, human immunodeficiency virus-related neuropathy), hereditary conditions, trauma, nerve entrapment (e.g., carpal tunnel syndrome), collagen-vascular disorders, toxic agents, and cancer.[68] Yet, in many cases, the cause of the neuropathy is unknown.[67,89] Clinically, PN often manifests as weakness, numbness, paresthesias (abnormal sensations, such as pins and needles, burning, tingling, or prickling), and pain in the hands, arms, legs, or feet.[67] Treatment of the PN depends on the underlying cause and includes medications, physical approaches (e.g., PT, electroanalgesia, cold and heat), psychological approaches (including education about management of the underlying condition), and in some cases, surgery (Tables 39 and 42).[67-68]

f. Headache

Headache includes migraine with and without aura, tension-type, and cluster headaches. Headache disorders may be acute, chronic, or both, but are classified as chronic for the purpose of this discussion. Symptoms, triggers, and treatment vary with headache type. Migraine without aura (formerly common migraine) is an idiopathic chronic headache disorder characterized by a unilateral, pulsating headache of moderate to severe intensity. The headache ranges in duration from 4 to 72 hours and is accompanied by various symptoms (e.g., photophobia, nausea, vomiting).[79] Migraine with aura (formerly classic migraine) is similar but is preceded by transient

Table 42. Nonpharmacologic Interventions for Chronic Noncancer Pain

Type of Pain	Surgical	Other Physical Methods	Psychological Methods	Other
Arthritis pain	Includes arthroscopy and TJR for OA[a] and synovectomy, osteotomy, spinal fusion, and arthroscopy and TJR for RA	TENS, applied heat or cold, low-impact aerobic and ROM exercises, joint protection (splint or brace), massage, PT, OT	PE (rest, exercise, nutrition) and social support	Acupuncture Nutritional supplements[b]
Low back pain	For example, laminectomy, diskectomy, lumbar fusion, lumbar stabilization[c]	SCS, cryoanalgesia, radiofrequency coagulation, exercise (for strength and flexibility), PT, OT, TENS, braces, vibration	PE, "back school," biofeedback, psychotherapy	Acupuncture Manipulation therapy
Fibromyalgia		Applied heat, massage, gentle aerobic exercise and stretching, attention to proper posture, PT, TENS, vibration	PE, relaxation, hypnosis, psychotherapy	Acupuncture[d]
Sickle cell disease		Careful hydration, applied heat, massage, ultrasound, PT, TENS	PE, deep breathing and relaxation techniques, distraction, imagery, hypnosis, meditation, biofeedback, psychotherapy	Acupuncture/ acupressure
Peripheral neuropathy (e.g., PDN, PHN)	For example, decompressive surgery for nerve entrapment, vascular surgery for vascular insufficiency	Good skin care and foot care, PT, TENS, possibly SCS, applied heat or cold, massage	PE (e.g., need for tight blood glucose control, good skin and foot care), relaxation, biofeedback, psychotherapy	
Migraine and other types of headache		Application of heat or cold, exercise (prophylaxis), vibration	PE (triggers, medication compliance), relaxation and biofeedback (thermal, EMG training) for headache prophylaxis	

Sources: References 49-52, 54-56, 58, 60, 65, 67-68, 86, and 88-89.

[a]Surgery for OA is for patients with moderate to severe pain and functional disability who have not responded to medical therapy.[5] Total joint arthroplasty usually is associated with a good outcome and improved quality of life.[85]

[b]Not currently recommended due to lack of data. Trials for some supplements (glucosamine and chrondroitin sulfate) are underway.[51]

[c]The Food and Drug Administration has approved medical devices such as the Intervertebral Body Fusion device, Anterior Spinal Implant, and Posterior Spinal Implant to treat degenerative disk disease and stabilize and fuse the spine.[86]

[d]Usually reserved for patients with fibromyalgia syndrome/myofascial pain syndrome who do not respond to other measures.[56,87]

EMG: electromyography; OA: osteoarthritis; OT: occupational therapy; PDN: painful diabetic neuropathy; PE: patient education; PHN: postherpetic neuralgia; PT: physical therapy; RA: rheumatoid arthritis; ROM: range of motion; SCS: spinal cord stimulation; TENS: transcutaneous electrical nerve stimulation; TJR: total joint replacement.

neurologic symptoms (e.g., visual disturbances, aphasia, hemiparesis). Tension-type headache refers to a bilateral pressing or tightening type of headache of mild to moderate severity, which may be episodic or chronic.[79] Cluster headaches are unilateral headaches usually located around the eye (periorbital). Patients may experience excruciating boring, knife-like, or burning pain, tearing, and rhinorrhea. The attacks are relatively short but may recur numerous times a day.[79] Treatment of migraine includes medications (abortive and prophylactic), physical approaches (e.g., cold and heat), psychological approaches (e.g., relaxation, biofeedback), and in some cases, regional anesthesia (Tables 40 to 42).[71-78]

Section V:

Strategies to Improve Pain Management

A. Clinical Practice Guidelines

1. Which Practice Guidelines Apply to Pain Management?

The Agency for Health Care Policy and Research (AHCPR)[a] introduced the first clinical practice guideline (CPG) for pain management in 1992.[1] Other groups, including the American Pain Society (APS), the American Society of Anesthesiologists (ASA), and the American Academy of Family Physicians (AAFP), have since produced an assortment of CPGs relevant to the management of acute and chronic pain (Table 43). In addition, numerous disciplines have developed CPGs relevant to specific types of pain or the management of conditions with a painful component (Table 44).

[a] The Agency for Health Care Policy and Research is now the Agency for Healthcare Research and Quality.

Table 43. Examples of Practice Guidelines for Management of Acute or Chronic Pain

Year	Source	Title
1992	AHCPR[a]	Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1 (Publication No. 92-0032)
1993	AHCPR[a]	Acute Pain Management In Adults: Operative Procedures Quick Reference Guide for Clinicians No. 1a (Publication No. 92-0019)
1995	ASA	Practice guidelines for acute pain management in the perioperative setting
1996	ASA	Practice guidelines for sedation and analgesia by non-anesthesiologists
1997	ASA	Practice guidelines for chronic pain management
1997 (revised 1999)	UIGNIC	Acute pain management
1998	AGS	The management of chronic pain in older persons
1999	APS	Principles of analgesic use in the treatment of acute pain and cancer pain
1999	AMDA	Chronic pain management in the long-term care setting
2000	AAFP	Treatment of nonmalignant chronic pain
2000	ICSI	Assessment and management of acute pain

Sources: Reference 1-11.

[a]The Agency for Health Care Policy and Research is now the Agency for Healthcare Research and Quality.

AAFP: American Academy of Family Physicians; AGS: American Geriatrics Society; AHCPR: Agency for Health Care Policy and Research; AMDA: American Medical Directors Association; APS: American Pain Society; ASA: American Society of Anesthesiologists; ICSI: Institute for Clinical Systems Improvement; UIGNIC: University of Iowa Gerontological Nursing Interventions Center.

Table 44. Examples of Practice Guidelines for the Management of Specific Types of Pain or Conditions With Painful Components

Year	Source	Title
1994	AHCPR[a]	Clinical Practice Guideline: Management of Cancer Pain (Publication No. 94-0592)
1994	AHCPR[a]	Acute Low Back Problems in Adults Guideline No. 14 (Publication No. 95-0642)
1995	ACR	Guidelines for the medical management of osteoarthritis Part I. Osteoarthritis of the hip
1995	ACR	Guidelines for the medical management of osteoarthritis Part II. Osteoarthritis of the knee
1996	ACR	Guidelines for the management of rheumatoid arthritis
1996	ASA	Practice guidelines for cancer pain management
1997	NIH	Acupuncture. NIH Consensus Statement
1999	ICSI	Adult low back pain
1999	ASA	Practice guidelines for obstetrical anesthesia
1999	SNM	Procedure guideline for bone pain treatment
1999	AAOS	Clinical guideline on hip pain
1999	AAOS	Clinical guideline on knee pain
1999	AAOS	Clinical guideline on wrist pain
1999	APS	Guideline for the management of acute and chronic pain in sickle cell disease
1999, 2000	AAN	Evidence-based guidelines for migraine headache (series)
2000	AAFP	Guidelines on migraine (series)
2000	AAFP	Osteoarthritis: current concepts in diagnosis and management
2000	AAFP	Management of pain in sickle cell disease
2000	ICSI	Health care guideline. Migraine headache
2000	ICSI	Health care guideline. Diagnosis and treatment of adult degenerative joint disease (DJD) of the knee

Sources: References 12-39.

[a]The Agency for Health Care Policy and Research is now the Agency for Healthcare Research and Quality.

AAN: American Academy of Neurology; AAOS: American Academy of Orthopaedic Surgeons; ACR: American College of Rheumatology; AHCPR: Agency for Health Care Policy and Research; AAFP: American Academy of Family Physicians; ASA: American Society of Anesthesiologists; ICSI: Institute for Clinical Systems Improvement; NIH: National Institutes of Health; SNM: Society of Nuclear Medicine.

2. Are Clinicians Adopting and Using Clinical Practice Guidelines?

Pain management remains inadequate, despite the availability of CPGs. To clarify the basis of this problem, various studies have explored clinicians' adoption and use of CPGs or the effects of a specific CPG initiative on clinical practice. Table 45 summarizes some of these studies. Overall, these data suggest that, despite some improvements, inconsistent assessment and inappropriate treatment of pain (e.g., intramuscular injections) persist.[41,45] Furthermore, administrative mandates rather than education alone appear necessary to change practice patterns.[48]

Table 45. Examples of Studies of Guideline Adherence and Interventions

Source	Purpose	Methods	Findings and Conclusions
Pellegrini et al, 1999	Assess compliance with AHCPR guidelines in prescribing meperidine for obstetrical patients	Review of 300 charts of obstetric patients	Of 157 obstetrical patients receiving meperidine, 124 (79.8%) were not treated in accordance with AHCPR guidelines. The most frequent conflicts with the guidelines were suboptimal dosing and the treatment of chronic pain.
Carr et al, 1998	Assess compliance with AHCPR and ASA guidelines	National survey of pain in perioperative patients	Overall adherence was excellent except for continuing frequent intramuscular administration of opioids and infrequent use of nonpharmacologic pain management methods
Data Strategic Benchmarks, 1999	Assess compliance with AHCPR guidelines for management of postoperative pain	Review of records from multiple Wisconsin hospitals	Data from a multi-hospital study shows low compliance with pain management protocols for postoperative pain.
Cleeland et al, 1994	Assess compliance with WHO analgesic guidelines in managing cancer pain	Survey of 1308 outpatients with metastatic cancer treated at 54 sites affiliated with ECOG	42% of patients reported receiving insufficient analgesics; inadequate pain control was higher among some groups (e.g., racial minorities, women, elderly).
Cleeland et al, 1997	Assess compliance with guideline-recommended analgesic prescriptions for cancer in clinic setting	Survey of minority cancer patients	65% of minority cancer patients did not receive guideline-recommended analgesic prescriptions compared with 50% of non-minority patients.
Stratis Health, 1997	Assess compliance with AHCPR and American Pain Society guidelines for assessing cancer pain	Review of records for 271 cancer patients treated in Minnesota hospitals	Whereas 93% of the hospitals had documented some form of the patient's initial self-assessment of pain, only 26% used effective means of communicating pain intensity. Pain reassessment was also inconsistent.
Rischer and Childress, 1996	Assess whether the implementation of an AHCPR guideline-based action plan would improve pain and satisfaction among cancer patients	Chart audits at seven acute care hospitals in Utah before and after implementation	Process measures of care showed improved compliance with guidelines for managing cancer pain post-intervention; however, investigators concluded that "more needed to be done to prevent patient suffering."
Du Pen et al, 1999	Assess whether the implementation of an AHCPR guideline-based treatment algorithm for cancer pain would improve pain management in the community setting	Comparison of pain and symptom management in 81 cancer outpatients treated according to algorithm or standard-practice (control)	Cancer patients in the treatment algorithm group experienced a significant reduction in usual pain intensity compared with controls. The investigators concluded that comprehensive pain assessment and evidence-based analgesic decision-making processes enhance usual pain outcomes.
Harwood et al, 1997	Assess whether an AHCPR guideline-based educational program would improve the assessment of new low back pain by physicians	Compliance with the assessment protocol was measured by computer-based surveillance; the educational program included group and individual sessions, with extensive follow-up	An administrative mandate to change, but not the educational program alone, resulted in a significant increase in physician compliance in completing a standardized examination (assessment) for low back pain.

Sources: References 40-48.

AHCPR: Agency for Health Care Policy and Research (now the Agency for Health Care Research and Quality); ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization.

B. Standards and Outcome Measures

1. JCAHO Standards

Various groups (e.g., the Joint Commission on Accreditation of Healthcare Organizations [JCAHO], APS, ASA) have proposed standards, outcome measures, and other initiatives in efforts to improve pain management (Table 46). Outcome measures complement CPGs because they help quantify the effects of a given therapy on the patient's health and well-being. Combined with other data (e.g., measures of guideline adherence), health care organizations can use outcome data to evaluate and optimize provider performance. Standards provide a clear definition of what appropriate care entails; thus, they also improve quality of care.

Of these strategies, the recently introduced JCAHO standards for pain management have attracted the most attention. The standards clearly outline appropriate pain management practices for ambulatory care facilities, behavioral health care facilities, health care networks, home care, hospitals, long-term care organizations, long-term care pharmacies, and managed behavioral health care organizations seeking accreditation.[49] These new standards are available on the World Wide Web (http://www.jcaho.org), and the second monograph in this series discusses these standards in greater detail. Briefly, the standards call upon organizations and facilities to:

- Recognize the right of patients to appropri-

Table 46. Examples of New Outcome Measures, Standards, and Initiatives Related to Pain Management

Organization	What Is Being Done	Purpose
ASA Committee on Pain Management	Recent development of pain outcome assessment questionnaire called the "ASA Nine"; this questionnaire considers nine items (domains) in assessing the efficacy of pain therapy	To measure outcomes in patients receiving pain therapy from anesthesiologists
APS	Pain as the 5th Vital Sign initiative (i.e., measure pain as a fifth vital sign with each evaluation of the standard four vital signs [i.e., temperature, pulse, respiration, and blood pressure])	Pain management improvement strategy directed at raising clinician awareness of need to assess pain regularly
APS	Alteration of WHO analgesic ladder	To make WHO ladder a more appropriate form of guidance, which recognizes that pain should be assessed for severity and treated with adequate analgesia in a timely manner
VHA National Pain Management Strategy	Initiative calling for a series of assessments to be performed by clinicians, including regular assessment of pain intensity with the NRS	To prevent pain and suffering in individuals receiving care in the VHA system
HCFA	Current evaluation of outcome measures to be used by hospice workers for assessing patient comfort during the dying process	To improve the quality of pain management at end of life for Medicare and Medicaid beneficiaries
HCFA	Recent identification of pain management at the end of life as a PRO program priority	Proposed project will implement an intervention to increase quality of care with respect to pain management and comfort in a population and setting where there is a demonstrated need[a]
JCAHO	Inclusion of new standards for pain assessment and management in JCAHO standards	To provide standards of care to be followed by ambulatory care facilities, behavioral health care facilities, health care networks, home care, hospitals, long-term care organizations, long-term care pharmacies, and managed behavioral health care organizations
NCQA	Involved in developing outcome measures related to pain management	Advance assessment of pain outcomes

[a]A population with a "demonstrated need" includes patients with cancer, congestive heart failure, chronic obstructive pulmonary disease, human immunodeficiency virus infection, aquired immunodeficiency syndrome, diabetes, end-stage renal disease, or another progressive illness.

APS: American Pain Society; ASA: American Society of Anesthesiologists; HCFA: Health Care Financing Administration; JCAHO: Joint Commission on Accreditation of Healthcare Organizations; NCQA: National Committee for Quality Assurance; NRS: Numeric Rating Scale; PRO: peer-reviewed organization; VHA: Veteran's Healthcare Administration; WHO: World Health Organization

ate assessment and management of pain
- Screen for the presence and assess the nature and intensity of pain in all patients
- Record the results of the assessment in a way that facilitates regular reassessment and follow-up
- Determine and ensure staff competency in pain assessment and management (e.g., provide education), and address pain assessment and management in the orientation of all new clinical staff
- Establish policies and procedures that support the appropriate prescribing or ordering of pain medications
- Ensure that pain does not interfere with a patient's participation in rehabilitation
- Educate patients and their families about the importance of effective pain management
- Address patient needs for symptom management in the discharge planning process
- Incorporate pain management into performance review activities (i.e., establish a means of collecting data to monitor the appropriateness and effectiveness of pain management)

2. Institutional Commitment to Pain Management

Whereas the new JCAHO standards tell organizations what needs to occur in the assessment and management of pain, they do not tell organizations how to do it. Because education alone does not change practice patterns, health care organizations and institutions need to support system changes to improve pain management and comply with the new JCAHO standards. That is, in addition to providing staff with practical clinical resources for pain management, health care organizations and institutions need to make pain "visible" and establish mechanisms to ensure accountability for pain control.[50] The book *Building an Institutional Commitment to Pain Management: Wisconsin Resource Manual* describes key steps to "institutionalizing" effective pain management, as summarized in Table 47.[50] In addition, the second monograph in this series reviews organizational performance measurement and improvement related to pain management to facilitate organizational initiatives.

Table 47. Building an Institutional Commitment to Pain Management

- Develop an interdisciplinary work group to promote practice change and collaborative practice. At a minimum, this work group should consist of representatives (clinicians, administrators) from medicine, nursing, and pharmacy, with those from other disciplines (e.g., OT, PT, RT, social work, pastoral care) when possible. Levels of experience should range from experts to novice.
- Analyze current pain management issues and practices in the health care setting, with the goal of continuous quality improvement. Plan a needs assessment to collect information about the quality of pain management and to identify causes of inadequate pain management. Sources of data include systematic observation of current practice, patient and staff surveys, medical record audits, and drug utilization reviews.
- Articulate and implement a standard for pain assessment and documentation to ensure the prompt recognition, documentation, and treatment of pain. This standard should define:
  1) how, when, and by whom pain should be assessed;
  2) where the results should be documented;
  3) methods of communicating this information among caregivers; and
  4) explicit conditions for interventions directed at relieving pain.
- Establish explicit policies and procedures to guide the use of specialized techniques for administering analgesics (e.g., intraspinal and intravenous analgesia and anesthesia, inhalational therapy, conscious or deep sedation).
- Establish accountability for quality pain management. This should include clearly defining caregiver responsibilities in pain management and embedding accountability for pain management in existing systems (e.g., practice standards, position descriptions, policies and procedures, competency statements, performance reviews).
- Provide readily available information about pharmacologic and nonpharmacologic interventions to clinicians to facilitate planning of care (e.g., order writing, interpretation and implementation of physician orders). This information can be presented in a variety of formats including clinical practice guidelines and pathways, decision or treatment algorithms, protocols, pocket reference guides, and computer help screens.
- Promise patients a prompt response to their reports of pain. According to the APS guidelines for quality improvement of pain management, all patients at risk for pain should be informed that: 1) effective pain relief is important to treatment, 2) their report of pain is essential, and 3) staff will promptly respond to patient requests for pain treatment.[51] Therefore, patients and their families should be provided appropriate educational materials that address important aspects of pain assessment and management (e.g., the importance of controlling pain, the use of pain rating scales to report pain intensity, how to establish realistic pain relief goals, pharmacologic and non-pharmacologic interventions for pain)
- Provide education about pain management to staff. This education may be provided in a variety of formats, including orientation and continuing education programs; rounds, lectures, and case conferences; self-directed learning packages, case studies, and interactive techniques (e.g., brainstorming, role playing, experiential techniques, games).
- Continually evaluate and work to improve the quality of pain management.

Source: References 50-51.

APS: American Pain Society; OT: occupational therapy; PT: physical therapy; RT: recreation.

Glossary of Abbreviations and Acronyms

AAFP: American Academy of Family Physicians.

AAPM: American Academy of Pain Medicine.

AEDs: Antiepileptic drugs.

AHCPR: Agency for Health Care Policy and Research; now known as the Agency for Healthcare Research and Quality (AHRQ).

AHRQ: Agency for Healthcare Research and Quality; formerly known as the Agency for Health Care Policy and Research (AHCPR).

APS: American Pain Society.

ASA: American Society of Anesthesiologists.

ASAM: American Society of Addiction Medicine.

ATC: Around-the-clock.

BPI: Brief Pain Inventory.

CARF: Commission on Accreditation of Rehabilitation Facilities.

CBT: Cognitive behavioral therapy.

CNCP: Chronic noncancer pain

CNMP: Chronic nonmalignant pain

CNS: Central nervous system

COX: Cyclooxygenase

CPGs: Clinical practice guidelines.

CPMP: Chronic pain management program.

CPS: Chronic pain syndrome

DH: Dorsal horn

ECG: Electrocardiogram.

EEAs: Excitatory amino acids

EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine).

FPS: Faces Pain Scale.

FSMB: The Federation of State Medical Boards of the United States.

GABA: γ-Aminobutyric acid, which is an inhibitory neurotransmitter.

GI: Gastrointestinal.

HIV: Human immunodeficiency virus.

IASP: International Association for the Study of Pain.

IM: Intramuscular.

IV: Intravenous.

JCAHO: Joint Commission on Accreditation of Healthcare Organizations.

LAs: Local anesthetics.

LBP: Low back pain.

MPQ: McGill Pain Questionnaire.

NMDA: N-methyl, D-aspartic acid.

NRS: Numeric rating scale.

NSAIDs: Nonsteroidal anti-inflammatory drugs.

OA: Osteoarthritis.

OT: Occupational therapy.

PCA: Patient-controlled anesthesia

PGs: Prostaglandins.

PN: Peripheral neuropathy.

PO: Per os (oral).

PRN: As needed.

PT: Physical therapy.

RA: Rheumatoid arthritis.

SCD: Sickle cell disease.

TCAs: Tricyclic antidepressants.

TENS: Transcutaneous electrical nerve stimulation.

VAS: Visual analog scale.

VHA: Veterans Health Administration.

Glossary of definitions

A-δ nociceptors: Nociceptors associated with relatively rapidly conducting A-delta fibers.

abstinence syndrome: A syndrome that may occur with abrupt cessation or diminution of chronic drug administration; the nature and time of onset of this syndrome vary with drug actions and half-life.

activation: Excitation of a neuron sufficient to generate a nerve impulse (action potential).

addiction: A primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations; addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

adjuvant analgesic: A medication that is not a primary analgesic but that has independent or additive pain-relieving effects.

agonists: Agents that exert pharmacologic effects by binding to and activating stereospecific receptors.

allodynia: Pain caused by a stimulus that normally does not provoke pain.

analgesia: Absence of pain.

analgesic ceiling: A dose of an analgesic beyond which no additional analgesia is obtained.

ankylosing spondylitis: Ankylosing (fusing together) spondylitis (spinal inflammation) is a type of arthritis that affects the spine.

antagonists: Agents that competitively bind with the binding sites of agonists and thereby inhibit the agonist's actions.

arachnoiditis: Inflammation and thickening of the arachnoid membrane (one of three membranes covering the central nervous system) around nerve roots.

atelectasis: The absence of gas in part or all of lung (i.e., partial or complete lung collapse).

autonomic responses: See sympathetic (nervous system) hyperactivity.

biofeedback: The process of training a person (or animal) to regulate physiologic responses by providing feedback (typically sounds or light patterns) about those responses. Clinically, patients are typically taught to control finger temperature, perspiration, muscle tension, and other responses.

breakthrough pain: Pain that "breaks through" pain relief provided by ongoing analgesics.

C-nociceptors: Nociceptors associated with slowly conducting unmyelinated C-fibers.

central nervous system (CNS): Consists of the brain and spinal cord.

central sensitization: Enhanced excitability and responsiveness of spinal neurons.

cerebral cortex: Gray cellular "mantle" of the brain, which includes the sensory cortex, motor cortex, and association cortex.

chronic noncancer pain (CNCP): Persistent pain that is not associated with cancer.

chronic nonmalignant pain (CNMP): Persistent pain that is not attributable to a life-threatening condition; some prefer to use alternate terms (i.e., chronic noncancer pain, chronic non-cancer–related pain).

chronic pain syndrome (CPS): Psychosocial disorder that occurs in some patients with chronic noncancer pain in which symptoms of the pain consume the attention of and incapacitate the patient.

continuous dysesthesia: A continuous type of neuropathic pain that manifests as burning, electrical, or other abnormal sensations.

cyclooxygenase (COX): Enzyme involved in prostaglandin synthesis; there are two isoforms: COX-1 and COX-2.

deep somatic pain: A type of somatic pain associated with ongoing activation of nociceptors in muscles, tendons, joint capsules, fasciae, or bones.

deep tissues: Tissues including bone, muscle, tendons, joint capsules, and fasciae.

dermatomes: Cutaneous sensory pathways that are defined by sensation; each dermatome corresponds to the area of skin that is supplied by the dorsal roots of a particular sensory nerve.

dorsal horn (DH): The posterior gray matter of the spinal cord, which contains cell bodies or neurons; the spinal cord consists of 10 laminae (segments), and laminae I-VI comprise the dorsal horn.

dorsal horn neurons: Neurons in the dorsal horn of the spinal cord, including interneurons and second order (projection) neurons.

dysesthesia: An unpleasant abnormal sensation, which may be spontaneous or evoked.

endogenous opioids: Natural opioids produced by the body; also referred to as enkephalins and endorphins.

epidural: Situated on the outside of the dura mater (a tough lining that surrounds the spinal cord).

equianalgesic: Having an equivalent analgesic effect.

equianalgesic dose chart: A chart that is used to convert from one analgesic or route of administration to another. Such charts typically describe the dose of an opioid required to produce the same degree of pain relief provided by a standard oral or parenteral dose of morphine.

excitatory amino acids (EAAs): These include the neurotransmitters glutamate and aspartate, which mediate most excitatory transmission in the central nervous system.

glutamate: An excitatory amino acid neurotransmitter responsible for much of excitatory transmission in the central nervous system.

hyperalgesia: An abnormally painful response to a stimulus.

hyperpathia: An abnormally painful and exaggerated response to a stimulus, especially a repetitive stimulus.

iatrogenic: A response to a medical or surgical treatment induced by the treatment itself.

inflammation: A pathologic process involving complex chemical and cellular reactions that occurs in tissues in response to injury or abnormal stimulation. Its cardinal signs— rubor (redness), calor (heat or warmth), tumor (swelling), and dolor (pain)—reflect processes directed at destroying/removing injurious material and at promoting repair and healing.

inflammatory mediators: Inflammatory mediators include prostaglandins, bradykinin, serotonin, and histamine.

ischemia: A reduction in local blood flow due to obstruction of the blood supply.

lancinating pain: A type of neuropathic pain that manifests as an episodic shooting, stabbing, or knifelike pain.

limbic system: The limbic system includes structures such as the amygdala, hippocampus, septal nuclei, hypothalamus, and transitional cortical regions (e.g., cingulate gyrus). This part of the brain is involved with emotional responses.

mu agonists: Opioids that bind to m_1 and m_2 receptors in the brain, spinal cord, and under certain conditions

(i.e., inflammation), the periphery to exert their effects.

multimodal analgesia: Also known as "balanced analgesia," this approach to pain management involves the use of more than one method or modality of controlling pain (e.g., drugs from two or more classes, drug plus nondrug treatment) to obtain additive beneficial effects, reduce side effects, or both.

neuroablation: Destruction of tissue, typically by surgical, chemical (phenol), or heat (radiofrequency) lesions; the goal of neuroablative surgeries is to interrupt signal flow between peripheral sources of pain and the brain or to remove neural structures that contribute to pain.

neurolysis: A technique for destroying neural tissue that involves injection of a destructive chemical or use of cold (cryotherapy) or heat (radiofrequency coagulation).

NMDA receptors: A type of glutamate receptor involved in mediating excitatory neurotransmission; these receptors are thought to play an important role in central sensitization.

nociceptors: Sensory receptors that are preferentially sensitive to tissue trauma or a stimulus that would damage tissue if prolonged.

parenteral administration: Administration of a drug via a route other than the gastrointestinal system, such as by intravenous, intramuscular, or subcutaneous injection.

paresthesia: An abnormal sensation (e.g., "pins and needles" from a foot "going to sleep"), which may be spontaneous or evoked.

patient-controlled anesthesia (PCA): The self-administration of analgesics by a patient; often involves an intravenous, subcutaneous, or epidural opioid administered via a pump.

perioperative pain: Pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources.

peripheral sensitization: A lowering of the stimulus (pain) threshold for nociceptor activation and an increase in the frequency of nerve impulse firing.

physical dependence: A state of adaptation that often includes tolerance and is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the drug, and/or administration of an antagonist.

potency: The dose of a drug required to produce a particular effect (e.g., pain relief).

preemptive analgesia: A pharmacologic intervention performed before a noxious event (e.g., surgery) that is intended to minimize the impact of the stimulus by preventing peripheral and central sensitization.

primary afferent (nerve) fibers: Axons of primary afferent (or "first order") neurons that transmit impulses from the periphery toward the central nervous system. Each neuron has a cell body that resides in sensory ganglia (e.g., dorsal root ganglia) and a bifurcated axon. One branch extends along a peripheral nerve and ends in a sensory receptor; the other branch projects to the spinal cord, where it synapses with a spinal neuron (e.g., interneuron, projection neuron).

projection neurons: Neurons in the dorsal horn of the spinal cord with nerve fibers that project to the brain in tracts; these neurons are responsible for transmitting nociceptive information from the spinal cord to higher centers.

pseudoaddiction: Patient behaviors that may occur when pain is undertreated (e.g., increased focus on obtaining medications or "drug seeking," "clock watching," use of illicit drugs, or deception) and that can be mistaken for true addiction.

responsiveness: The probability of achieving adequate pain relief with an analgesic without encountering unmanageable side effects.

somatic pain: Pain arising from tissues such as skin, muscle, tendon, joint capsules, fasciae, and bone.

somatosensory cortex: A subdivision of the sensory cortex.

spinothalamic tract (STT): Major pathway by which nociceptive information travels from the dorsal horn of the spinal cord to the thalamus.

"stress hormone" response: A series of responses to an acute injury or stress that leads to an increase in the metabolic rate, blood clotting, and water retention; impaired immune function; and a "fight or flight" alarm reaction with autonomic features. These responses minimize further damage and blood loss, promote healing, prevent or fight infection, and reduce blood flow to vital organs, among other functions.

substance P: A neuropeptide that activates spinal neurons and enhances their responsiveness to excitatory amino acids, thus facilitating nociception.

superficial (cutaneous) somatic pain: A type of somatic pain associated with ongoing activation of nociceptors in the skin, subcutaneous tissue, or mucous membranes.

sympathetic (nervous system) hyperactivity: Symptoms and signs of sympathetic (autonomic) nervous system hyperactivity include increased heart rate, blood pressure, and respiratory rate; sweating; pallor; dilated pupils; nausea; vomiting; dry mouth; and increased muscle tension.

tolerance: A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

visceral pain: Pain arising from visceral organs (e.g., heart, lungs, gastrointestinal tract, liver, gallbladder, kidneys, bladder).

References Section I: Background and Significance

1. Gallup survey conducted by the Gallup Organization from May 21 to June 9, 1999. Supported by the Arthritis Foundation and Merck & Company, Inc.
2. Fox CD, Berger D, Fine PG, et al. Pain assessment and treatment in the managed care environment. A position statement from the American Pain Society. Glenview, IL: American Pain Society; 2000.
3. National Pain Survey. Conducted for Ortho-McNeil Pharmaceutical,1999.
4. American Pain Foundation. Facts about pain. Available at: http://www.painfoundation.org/page_fastfacts.asp. Accessed September 2001.
5. Brookoff D. Chronic pain: 1. A new disease? Hospital Practice. Available at: www.hosppract.com/issues/2000/07/brook.htm. Accessed June 2001.
6. Teoh N, Stjernsward J. WHO cancer pain relief program: ten years on. IASP Newsletter, 1992.
7. Brookoff D. Chronic pain: 2. The case for opioids. Hospital Practice. Available at: www.hosppract.com/issues/2000/09/brook.htm. Accessed June 2001.
8. American Pain Society Quality of Care Committee. Quality improvement guidelines for the treatment of acute pain and cancer pain. JAMA. 1995;23:1874-1880.
9. Field MJ, Cassel CK, eds; Committee on Care at the End of Life. Approaching Death: Improving Care at the End of Life. Washington, DC: Institute of Medicine, National Academy Press; 1997.
10. Carr DB, Goudas LC. Acute pain. Lancet. 1999;2051-2058.
11. American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health and the American Pain Society Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents (0793). Available at: http://www.aap.org/policy/ 9933.html. Accessed September 2001.
12. Chronic Pain in America Survey. Conducted for American Pain Society, the American Academy of Pain Medicine, and Janssen Pharmaceutica, 1999.
13. Jacox AK, Carr DB, Chapman CR, et al. Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1. Rockville, MD: US Department of Health and Human Services, Agency for Health Care Policy and Research; 1992. AHCPR publication 92-0032.
14. American Pain Society. Chronic pain in America: roadblocks to relief. Available at: http://www.ampainsoc.org/ whatsnew/conclude-road.htm. Accessed June 2001.
15. Becker N, Bondegaard Thomsen A, Olsen AK, et al. Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. Pain. 1997;73:393-400.
16. Butler RJ, Hartwig R, Gardner HH. HMOs moral hazard and cost shifting in workers' compensation. J Health Econ. 1997;16:191-206.
17. Joint Commission on Accreditation of Healthcare Organizations. Pain management standards. Effective January 1, 2001. Available at: www.jcaho.org/standard/ pain_hap.html. Accessed September 2001.
18. McCaffery M. Nursing practice theories related to cognition, bodily pain and man-environmental interactions, Los Angeles, CA: 1968. UCLA Students Store.
19. Merskey H, Bugduk N. Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 2nd ed. Seattle, WA: IASP Press; 1994.
20. Fields HL. Pain. New York: McGraw Hill; 1987:364.
21. Besson JM, Chaouch A. Peripheral and spinal mechanism of nociception. Physiol Rev. 1987;67:67-186.
22. Chapman CR, Nakamura Y. A passion of the Soul: an introduction to pain for consciousness researchers. Conscious Cogn. 1999;8:391-422.
23. Pasero C, Paice JA, McCaffery M. Basic mechanisms underlying the causes and effects of pain. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:15-34.
24. Byers M, Bonica JJ. Peripheral pain mechanisms and nociceptor plasticity. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:26-72.
25. Meyer RA, Campbell JN, Raja SN. Peripheral neural mechanisms of nociception. In: Wall PD, Melzack R, eds. Textbook of Pain. 3rd ed. Edinburgh: Churchill Livingstone; 1994.
26. Woolf CJ. Recent advances in the pathophysiology of acute pain. Br J Anesthesiol. 1989;63:139-146.
27. Costigan M, Woolf CJ. Pain: molecular mechanisms. J Pain. 2000;1(3 suppl 1):35-44.
28. Woolf CJ. The pathophysiology of peripheral neuropathic pain-abnormal peripheral input and abnormal central processing. Acta Neuochir Suppl. 1993;58;125-130.
29. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature. 1971;234:231-238.
30. Smith JB, Willis AL. Aspirin selectively inhibits prostaglandin production in human platelets. Nat New Biol. 1971;231:235-237.
31. Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol. 1997;14:2-31.
32. Craig AD. Supraspinal pathways and mechanisms relevant to central pain. In: Case KL, ed. Pain and Central Nervous System Disease: The Central Pain Syndromes. New York: 1991:157-170.
33. Wilcox F. Excitatory neurotransmitters and pain. In: Bond MR, Charlton JE, Woolf CJ, eds. Pain Research and Clinical Management. Vol. 4. Proceedings of the VIth World Congress on Pain. Amsterdam: Elsevier; 1991:97-117.
34. Ueda H.In vivo molecular signal transduction of peripheral mechanisms of pain [review]. Jpn J Pharmacol. 1999;79(3):263-268.
35. Aimar P, Pasti L, Carmignoto G, et al. Nitric oxide-producing islet cells modulate the release of sensory neuropeptides in the rat substantia gelatinosa. J Neurosci. 1998;18(24):10375-10388.
36. Yaksh TL, Hua XY, Kalcheva I, et al. The spinal biology in humans and animals of pain states generated by persistent small afferent input [colloquium]. Proc Natl Acad Sci USA. 1999;96(14):7680-7686.
37. Randic M, Hecimovic H, Ryu PD. Substance P modulates glutamate-induced currents in acutely isolated rat spinal dorsal horn neurones. Neurosci Lett. 1990;117(1-2):74-80.
38. Coderre TJ, Katz J, Vaccarino AL, et al. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain. 1993;52:259-285.
39. Terman GW, Bonica JJ. Spinal mechanisms and their modulation. In: Loeser JD, Butler SH, Chapman CR, Turk DC, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:73-152.
40. Jeftiniaja S. Enkaphalins modulate excitatory synaptic transmission in the superficial dorsal horn by acting at mu-opioid receptors sites. Brain Res. 1988;460(2):260-268.
41. Hori Y, Endo K, Takahashi T. Presynaptic inhibitory action of enkephalin on excitatory transmission in superficial dorsal horn of the rat spinal cord. J Physiol (Lond). 1992;450:673-685.
42. Schneider SP, Eckert WA III, Light AR. Opioid-activated postsynaptic inward rectifying potassium currents in whole cell recordings in substantia gelatinosa neurons. J Neurophys. 1998;80(6):2954-2962.
43. Guilbaud G, Bernard JF, Besson JM. Brain areas involved in nociception and pain. In: Wall PD, Melzack R, eds. Textbook of Pain. 3rd ed. Edinburgh: Churchill Livingstone; 1994.
44. Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol. 1997;14:2-31.
45. Duggan AW, North RA. Electrophysiology of opioids. Pharmacol Rev. 1983;35:219-281.
46. Portenoy RK. Basic mechanisms. In Portenoy RK, Kanner RM, eds. Pain Management : Theory and Practice. Philadelphia: FD Davis; 1996:19-39.
47. Chapman CR. The psychophysiology of pain. In: Loeser JD, Butler SH, Chapman CR, Turk DC, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:461-477.
48. Covington EC. The biological basis of pain. Int Rev Psychiatry. 2000;12:128-147.
49. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971-979.
50. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci. 1984;7:309-338.
51. Hammond DL. Control systems for nociceptive afferent processing: the descending inhibitory pathways. In: Yasksh TL, ed. Spinal Afferent Processing. New York: Plenum Press; 1986:363-390.
52. Wallace K. The pathophysiology of pain. Crit Care Nurs Q. 1992;15(2):1-13.
53. Walsh TD. Antidepressants in chronic pain. Clin Neuropharmacol. 1983;6(4):271-295.

53a. Yaksh TL. Direct evidence that spinal serotonin and noradrenaline terminals mediate the spinal antinociceptive effects of morphine in the periaqueductal gray. Brain Res. 1979;160:180-185.

54. Schmidt RF, Schaible HG, Messlinger K, et al. Silent and active nociceptors: structure, functions, and clinical implications. In: Gebhart GF, Hammon DL, Jensen TS, eds. Progress in Pain Research and Management. Vol. 2. Seattle: IASP Press; 1994:235-247.
55. Neumann S, Doubell TP, Leslie T, et al. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. Nature. 1996;384:360-364.
56. Perl ER. Cutaneous polymodal receptors: characteristics and plasticity. Prog Brain Res. 1996;113:21-28.
57. Levine J, Taiwo Y. Inflammatory pain. In: Wall PD, Melzack R, eds. Textbook of Pain. Edinburgh: Churchhill Livingstone; 1994:45-56.
58. Alexander J, Black A. Pain mechanisms and the management of neuropathic pain. Curr Opin Neurol Neurosurg. 1992;5:228–234.
59. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis. 1998;5:209-227.
60. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature. 1983;306:686–688.

61. Mendell LM. Physiological properties of unmyelinated fiber projections to the spinal cord. Exp Neurol. 1966;16:316-332.
62. King AE, Thompson SW. Characterization of deep dorsal horn neurones in the rat spinal cord in vitro: synaptic and excitatory amino acid induced excitations. Comp Biochem Physiol A. 1989;93(1):171-175.
63. Price DD, Mao J, Mayer DJ. Central mechanisms of normal and abnormal pain sates. In: Fields HL, Liebeskind JC, eds. Progress in Pain Research and Management. Vol. 1. Seattle: IASP Press;1994:61-84.
64. MacDermott AB, Mayer ML, Westbrook GL, et al. NMDA-receptor activation increase cytoplasmic calcium concentration in cultured spinal cord neurons. Nature. 1986;321:519-522.
65. Yashpal K, Pitcher GM, Parent A, et al. Noxious thermal and chemical stimulation induce in-creases in 3 H-phorbol 12,13-dibutyrate binding in spinal cord dorsal horn as well as persistent pain and hyperalgesia, which is reduced by inhibition of protein kinase C. J. Neurosci. 1995;15:3263–3272.
66. Price DD, McHaffie JG, Larson MA. Spatial summation of heat-induced pain: influence of stimulus area and spatial separation of stimuli on perceived pain sensation and intensity and unpleasantness. J Neurophysiol. 1989;62:1270-1279.
67. Woolf, CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implication for the treatment of post-injury pain hypersensitivity states. Pain. 1991;44:293–299.
68. Yashpal K, Rakhakrishnan V, Coderre TJ, et al. CP-96,345, but not its stereoisomer, CP-96,344, blocks the nociceptive responses to intrathecally administered substance P and to noxious thermal and chemical stimuli in the rat. Neuroscience. 1993;52:1039–1047.
69. Ren K, Iadarola MJ, Dubner R. An isobolographic analysis of the effects of N-methyl-D-aspartate and NK1 tachykinin receptor antagonists on inflammatory hyperalgesia in the rat. Br J Pharmacol. 1996;117:196–202.
70. Ma QP, Allchorne AJ, Woolf CJ. Morphine, the NMDA receptor antagonist MK801 and the tachykinin NK1 receptor antagonist RP67580 attenuate the development of inflammation-induced progressive tactile hypersensitivity. Pain. 1998;77:49–57.
71. Woolf CJ, King AE. Dynamic alterations in the cutaneous mechanoreceptive fields of dorsal horn neurons in the rat spinal cord. J Neurosci. 1990;10:2717-2726.
72. Yaksh TL, Malmberg AB. Central pharmacology of nociceptive transmission. In: Wall PD, Melzack R, eds. Textbook of Pain. 3rd ed. Edinburgh: Churchill Livingstone; 1994.
73. Baranauskas G, Nistri A. Sensitization of pain pathways in the spinal cord: cellular mechanisms. Prog Neurobiol. 1998;54(3):349-65.
74. Yu XM, Salter MW. Src, a molecular switch governing gain control of synaptic transmission mediated by N-methyl-D-aspartate receptors. Proc Natl Acad Sci USA. 1999;96:7697-7704.
75. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci Lett. 1986;64:221-225.
76. McMahon SB, Wall PD. Receptive fields of rat lamina 1 projection cells move to incorporate a nearby region of injury. Pain. 1984;19:235-247.
77. Dickenson AH. Central acute pain mechanisms. Ann Med. 1995;27:223-227.
78. Cervero F, Laird JM, Pozo MA. Selective changes of receptive field properties of spinal nociceptive neurons induced by noxious visceral stimulation in the cat. Pain. 1992;51:335-342.
79. Ru-Rong JI, Woolf CJ. Neuronal plasticity and signal transduction in nociceptive neurons: Implications for the initiation and maintenance of pathological pain. Neurobiology Dis. 2001:8:1-10.
80. Hardy JD, Wolff HG, Goodell H. Experimental evidence on the nature of cutaneous hyperalgesia. J Clin Invest. 1950;29:115-140.
81. Woolf CJ. Pain. Neurobiol Dis. 2000;7:504-510.
82. McQuay H. Opioids in chronic pain. Br J Anaesth. 1989;63:213-226.
83. Wall PD. The prevention of postoperative pain. Pain. 1988;33:289-290.
84. Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. Pain. 1988;33:11-23.
85. Cherny NI, Thaler HT, Friedlander-Klar H, et al. Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: a combined analysis of controlled, single-dose studies. Neurology. 1994;44:857-861.
86. Covington EC. Anticonvulsants for neuropathic pain and detoxification. Cleveland Clin J Med. 1998;65(suppl 1):SI-21-SI-29.
87. Portenoy R. Mechanisms of clinical pain. Observations and speculations. Neurol Clin North Am. 1989;7:205-230.
88. Coda BA, Bonica JJ. General considerations of acute pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:222-240.
89. Gebhart GF, Ness TJ. Central mechanisms of visceral pain. Can J Physiol Pharmacol. 1991;69:627–634.
90. Meyer RA, Campbell JN, Raja SN. Peripheral neural mechanisms of cutaneous hyperalgesia. In: Fields HL, Dubner R, Cervero F, eds. Advances in Pain Research and Therapy. Vol. 9. New York: Raven; 1985:53-71.
91. Devor M. Neuropathic pain and injured nerve: peripheral mechanisms. Br Med Bull. 1991;47, 619–630.
92. Devor M. The pathophysiology of damaged peripheral nerves. In: Wall PD, Melzack R, eds. Textbook of Pain. 3rd ed. Edinburgh: Churchill Livingstone; 1994:79-100.
93. Inbal R, Rousso M, Ashur H, et al. Collateral sprouting in skin and sensory recovery after nerve injury in man. Pain. 1987;28:141-154.
94. Koltzenburg M. Painful neuropathies. Curr Opin Neurol. 1998;11:515-521.
95. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet. 1999;353:1959-1964.
96. Portenoy RK. Neuropathic pain. In Portenoy RK, Kanner RM, eds. Pain Management: Theory and Practice. Philadelphia: FD Davis; 1996:83-125.
97. Portenoy RK, Kanner RM. Definition and assessment of pain. In Portenoy RK, Kanner Rm, eds. Pain Management: Theory and Practice. Philadelphia: FD Davis; 1996:3-18.
97a. Portenoy RK. Management of neuropathic pain. In: Chapman CR, Foley K, eds. Current and Emerging Issues in Cancer Pain: Research and Practice. Lipincott-Raven; 1993: chapter 21. Available at: http://talaria.org/ch21.html#ch21.html_1. Accessed September 2001.
97b. Backonja MM. Painful Neuropathies. In: Loeser JD, Butler SH, Chapman CR, Turk DC, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:371-387.
97c. Galer BS, Schwartz L, Allen RJ. Complex regional pain syndromes—type I: reflex sympathetic dystrophy, and type II: causalgia. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:388-411.
97d. Tasker RR. Central pain states. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:433-457.
98. Turk DC, Okifuji A. Pain Terms and taxonomies of pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:17-25.
99. Jacobsen L, Mariano A. General considerations of chronic pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:241-254.
100. Dunajcik L. Chronic nonmalignant pain. In: McCaffery M, Pasero C, eds. Pain Clinical Manual, 2nd ed. St. Louis, MO: Mosby Inc; 1999:467-521.
101. Chapman CR, Stillman M. Pathological pain. In: Kruger L, ed. Pain and Touch. 2nd ed. New York: Academic Press; 1996:315-342.
102. Chapman CR, Foley K, eds. Current and Emerging Issues in Cancer Pain: Research and Practice. Lippincott-Raven; 1993. Available at: http://talaria.org/chtoc.html. Accessed September 2001.
103. Schappert SM. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1996. NCHS Vital Health Stat. 1998;13:1-37.
104. American Academy of Pain Medicine. FAQs about pain. Available at: http://www.painmed.org. Accessed April 2001.
105. Hitchcock LS, Ferrell BR, McCaffery M. The experience of chronic nonmalignant pain. J Pain Symptom Manage. 1994;9:312-318.
106. Marks RM, Sachar EJ. Undertreatment of medical inpatients with narcotic analgesics. Ann Intern Med. 1973;78:173-181.
107. Donovan M, Dillon P, McGuire L. Incidence and characteristics of pain in a sample of medical-surgical inpatients. Pain. 1987;30:69-78.
108. Oden R. Acute postoperative pain: Incidence, severity, and the etiology of inadequate treatment. Anesthesiol. Clin North Am. 1989;7:1-15.
109. Carr DB, Miaskowski C, Dedrick SC, Williams GR. Management of perioperative pain in hospitalized patients: a national survey. J Clin Anesth. 1998;10(1):77-85.
110. Abbott FV, Gray-Donald K, Sewitch MJ, Johnston CC, Edgar L, Jeans ME. The prevalence of pain in hospitalized patients and resolution over six months. Pain. 1992;50(1):15-28.
111. Gu X, Belgrade MJ. Pain in hospitalized patients with medical illnesses. J Pain Symptom Manage. 1993;8(1):17-21.
112. Ward SE, Gordon D. Application of the American Pain Society quality assurance standards. Pain. 1994;56:299-306.
113. Warfield CA, Kahn CH. Acute pain management: programs in U.S. hospitals and experiences and attitudes among U.S. adults. Anesthesiology. 1995;83:1090-1094.
114. Drayer RA, Henderson J, Reidenberg M. Barriers to better pain control in hospitalized patients. J Pain Symptom Manage. 1999;17(6):434-440.
115. Todd KH, Samaroo N, Hoffman JR. Ethnicity as a risk factor for inadequate emergency department analgesia. JAMA. 1993;269(12):1537-1539.
116. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med. 1994;330(9):592-596.
117. Zhukovsky DS, Gorowski E, Hausdorrf J, et al. Unmet analgesic needs in cancer patients. J Pain Symptom Manage. 1995;10(2):113-119.
118. Cleeland CS, Gonin R, Baez L, et al. Pain and treatment of pain in minority patients with cancer. The Eastern Cooperative Oncology Group Minority Outpatient Pain Study. Ann Intern Med. 1997;127(9):813-816.
119. Anderson KO, Mendoza TR, Valero V, et al. Minority cancer patients and their providers: pain management attitudes and practice. Cancer. 2000;88(8):1929-1938.
120. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. N Engl J Med. 2000;342(5):326-33.

121. Weiss SC, Emanuel LL, Fairclough DL, Emanuel EJ. Understanding the experience of pain in terminally ill patients. Lancet. 2001;357(9265):1311-1315.
122. Foley KM. Controlling cancer pain. Hospital Practice. Available at: http://www.hospprac.com/issues/20000/04/foley.htm. 2000. Accessed June 2001.
123. Anand KJ, Hickey PR. Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery. N Engl J Med. 1992;326(1):1-9.
124. Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after postoperative lumbar epidural blockade. Pain. 1988;33:297-301.
125. Tasmuth T, Estlanderb A, Kalso E. Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. Pain. 1996;68:343-347.
126. Foley KM. Pain syndromes in patients with cancer. In: Portenoy RK, Kanner RM, eds. Pain Management: Theory and Practice. Philadelphia: FA Davis; 1996:191-215.
127. Cherny NI, Portenoy RK. Practical issues in the management of cancer pain. In: Wall, PD, Melzack R, eds. Textbook of Pain. 3rd ed. Edinburgh: Churchill Livingstone; 1994:1437-1467.
128. Elliot KJ (presenter). Herpes zoster and postherpetic neuralgia: new pharmacological approaches to treatment and prevention. American Pain Society 15th Annual Scientific Meeting; Washington, DC; November 14-17,1996.
129. Desbiens NA, Wu AW, Alzola C, et al. Pain during hospitalization is associated with continued pain six months later in survivors of serious illnesses. Am J Med. 1997;103:269-276.
130. Walker LS, Garber J, Van Slyke DA, Greene JW. Long-term health outcomes in patients with recurrent abdominal pain. J Pediatr Psychol. 1995;20:233–245.
131. Bursch B. Pain in infants, children, and adolescents SIG. Policy statement on pediatric chronic pain. APS Bulletin. 2000;10(3). Available at: http://www.ampainsoc.org/pub/bulletin/may00/sig1.htm. Accessed September 2001.
132. Ferrell BR, Grant M, Chan J, et al. The impact of cancer education on family caregivers of elderly patients. Oncol Nurs Forum. 1995;22(8):1211-1218.
133. The NIH Guide: New Directions in Pain Research I. Washington, DC: U.S. Government Printing Office; 1998.
134. Gordon DB, Dahl JL, Stevenson KK . Introduction. In: Gordon DB, Dahl JL, Stevenson KK, eds. Building an Institutional Commitment to Pain Management. The Wisconsin Resource Manual. 2nd ed. Madison: University of Wisconsin-Madison Board of Regents; 2000.
135. Burke JP, Pestotnik SL, Classen DC, Lloyd JF. Evaluation of the financial impact of ketorolac tromethamine therapy in hospitalized patients. Clin Ther. 1996;18(1):197-211.
136. Pain and absenteeism in the workplace. Study conducted for Ortho-McNeil Pharmaceutical, 1997.
137. Association of Ottawa Anesthesiologists. Patient populations and pain syndromes to be treated. Chronic Pain Management Unit (CPMU). Available at: http://www.anesthesia.org/ pmu/pmu8.html. Accessed September 2001.
138. Jacox A, Carr DB, Payne R, et al. Management Of Cancer Pain: Adults Quick Reference Guide No. 9. Rockville, MD: U.S. Department of Human and Health Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 94-0593.
139. Booss J, Drake A, Kerns RD, Ryan B, Wasse L, . Pain as the 5th Vital Sign Toolkit. Geriatrics and Extended Care Strategic Healthcare Group, National Pain Management Coordinating Committee, Veterans Health Administration. Revised edition. October, 2000.
140. McCaffery M, Pasero C. Assessment: underlying complexities, misconceptions, and practical tools. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:35-102.
141. Berry PH, Dahl JL. Barriers to adequate pain management: an Ishikawa (Fishbone) diagram. Institutionalizing Pain Management Project. University of Wisconsin-Madison. 1998.
142. McCaffery M. Pain management: problems and progress. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:1-14.
143. President's Advisory Commission on Consumer Protection and Quality in the Health Care Industry. Quality First: Better Health Care for All Americans. Washington D.C.: U.S. Government Printing Office; 1998.
144. Jacox A, Carr DB, Payne R, et al. Clinical Practice Guideline: Management of Cancer Pain. Rockville, MD: US Department of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 94-0592.
145. Grossman SA, Scheidler VR, Sweeden K, et al. Correlation of patient and caregiver ratings of cancer pain. J Pain Symptom Manage. 1991;6:53-57.
146. Paice JA, Mahon SM, Faut-Callahan M. Factors associated with adequate pain control in hospitalized postsurgical patients diagnosed with cancer. Cancer Nurs. 1991;14:298-305.
147. Von Roenn JH, Cleeland CS, Gonin R, et al. Physician attitudes and practice in cancer pain management: a survey from the Eastern Cooperative Oncology Group. Ann Intern Med. 1993:119:121-126.
148. Heavner JE, Shi B, Diede J, et al. Acetaminophen (paracetamol) use and blood concentrations in pain patients. Pain Digest. 1996;6:215-218.
149. Burney KD, Krishnan K, Ruff MT, et al. Adherence to single daily dose of aspirin in a chemoprevention trial: An evaluation of self-report and microelectronic monitoring. Arch Fam Med. 1996;5:297-300.
150. Chapman CR. Compliance with pain medication: A hidden problem? APS Bulletin. 1996;6(6):11.
151. Pain & Policy Studies Group. Resource guide. Information about regulatory issues in pain management. Available at: http://www.medsch.wisc.edu/painpolicy/. Accessed February 2001.
152. American Society of Addiction Medicine. Definitions related to the use of opioids for the treatment of pain. Consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. February 2001. Available at: http://www.asam.org. Accessed June 2001.
153. Weissman DE, Burchman SL, Dinndorf PA, et al. Handbook of Cancer Pain Management. 2nd ed. Milwaukee, WI: Wisconsin Cancer Pain Initiative; 1990.
154. Joranson DE, Ryan KM, Gilson AM, et al. Trends in medical use and abuse of opioid analgesics. JAMA. 2000;283(13):1710-1714.
155. Newman RG. The need to redefine addiction. N Engl J Med. 1983;306:1096-1098.
156. Chapman CR, Hill HF. Prolonged morphine self-administration and addiction liability: evaluation of two theories in a bone marrow transplantation unit. Cancer. 1989;63:1636-1644.
157. Portenoy RK, Payne R. Acute and chronic pain. In: Lowinson JH, Ruiz P, Millman R, et al, eds. Comprehensive Textbook of Substance Abuse. Baltimore, MD: Williams & Wilkins; 1997.
158. Max MB, Payne R, Edwards WT, Sunshine A, Inturrisi CE, et al. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 4th ed. Glenview, IL: American Pain Society; 1999.
159. Haddox JD, Joranson D, Angarola RT, et al., The use of opioids for the treatment of chronic pain: a consensus statement from the American Academy of Pain Medicine and the American Pain Society. Glenview, IL: American Pain Society; 1997. Available at: http://www.ampainsoc.org/advocacy/opioids.htm. Accessed September 2001.
160. Federation of State Medical Boards of the United States, Inc. Model guidelines for the use of controlled substances for the treatment of pain. Euless, TX: author (tel: 817-868-4000). May 1998. Available at: http://www.fsmb.org/policy.htm. Accessed September 2001.
161. Federation of State Medical Boards of the United States, Inc. White paper in support of adoption of pain management guidelines. February 23, 2000. Available at: http://www.fsmb.org/policy.htm. Accessed September 2001.
162. Porter J, Jick H. Addiction rare in patients treated with narcotics [letter]. N Engl J Med. 1980;302:123.
163. Perry S, Heidrich G: Management of pain during debridement: a survey of US burn units. Pain. 1982;13:12-14.
164. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage. 1992;7(2):69-77.
165. McCaffery M, Ferrell BR. Nurses' knowledge of pain assessment and management: how much progress have we made? J Pain Symptom Manage. 1997;14:175-188.
166. O'Brien S, Dalton JA, Konsler G, et al. The knowledge and attitudes of experienced oncology nurses regarding the management of cancer-related pain. Oncol Nurse Forum. 1996;23:515-521.
167. Votherms R, Ryan P, Ward S. Knowledge of, attitudes toward, and barriers to pharmacologic management of cancer pain in a statewide random sample of nurses. Res Nurs Health. 1992;15:459-466.

References Section II: Assessment of Pain

1. Max MB, Payne R, Edwards WT, et al. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 4th ed. Glenview, IL: American Pain Society; 1999.
2. Campbell J. Pain as the 5th vital sign [presidential address]. American Pain Society, November 11, 1996.
3. Booss J, Drake A, Kerns RD, et al. Pain as the 5th Vital Sign Toolkit. Geriatrics and Extended Care Strategic Healthcare Group, National Pain Management Coordinating Committee, Veterans Health Administration. Revised edition. October 2000.
4. Joint Commission on Accreditation of Healthcare Organizations. Pain management standards. Effective January 1, 2001. Available at: www.jcaho.org/standard/pain_hap.html. Accessed September 2001.
5. Jacox AK, Carr DB, Chapman CR, et al. Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1. Rockville, MD: US Department of Health and Human Services, Agency for Health Care Policy and Research; 1992. AHCPR publication 92-0032.

6. Beecher HK. Limiting factors in experimental pain. J Chron Dis. 1956;4:11-12.
7. McCaffery M, Pasero C. Assessment: underlying complexities, misconceptions, and practical tools. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:35-102.
8. Loeser JD. Medical evaluation of the patient with pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:267-279.
9. Wilson PR, Caplan RA, Connis RT, et al, for the American Society of Anesthesiologists, Task Force on Pain Management, Chronic Pain Section. Practice guidelines for chronic pain management. Anesthesiology. 1997;86(4):995-1004.
10. Lewis T. Pain. New York: Macmillan; 1942:176.
11. Institute for Clinical Systems Improvement (ICSI) Work Group. ICSI Health Care Guideline. Assessment and Management of Acute Pain. September 2000.
12. Chapman CR, Syrjala KL. Measurement of pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:310-328.
13. Herr KA, Mobily PR, Kohout FJ, et al. Evaluation of the Faces Pain Scale for use with the elderly. Clin J Pain. 1998;14:29-38.
14. Szyfelbein SK, Osgood PF, Carr D. The assessment of pain and plasma beta-endorphin immunoactivity in burned children. Pain. 1985;2:173-182.
15. Beyer JE. Development of a new instrument for measuring intensity of children's pain. Pain. 1984;2(suppl):421.
16. Bieri D, Reeve R, Champion G, et al. The Faces Pain Scale for the self-assessment of severity of pain experienced by children: development, initial validation, and preliminary investigation for ratio scale properties. Pain. 1990;41:139-150.
17. Ready BL, Ashburn M, Caplan R, et al, for the American Society of Anesthesiologists, Task Force on Pain Management, Acute Pain Section. Practice guidelines for acute pain management in the perioperative setting. Anesthesiology. 1995;82(4):1071-8.
18. Dunajcik L. Chronic nonmalignant pain. In: McCaffery M, Pasero C. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:467-521.
19. Stolov WC. Electrodiagnostic evaluation of acute and chronic pain syndromes. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:279-296.
20. Baxter AF, Maravilla KR. Imaging pain patients. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:297-309.

20a. Buckley PF. Regional anesthesia with local anesthetics. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1893-1952.

21. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain. 1986;27:117-126.
22. Jensen MP, Turner LR, Turner JA, et al. The use of multi-item scales for pain intensity measurement in chronic pain patients. Pain. 1996;67:35-40.
23. Berthier F, Potel G, Leconte P, et al. Comparative study of methods of measuring acute pain intensity in an ED. Am J Emerg Med. 1998;16:132-136.
24. Paice JA, Cohen FL. Validity of a verbally administered pain rating scale to measure cancer pain intensity. Cancer Nurs. 1997;20:88-93.
25. Kremer E, Atkinson JH, Ignelzi RJ. Measurement of pain: patient preference does not confound pain assessment. Pain. 1981;10:241-248.
26. Revill SI, Robinson JO, Rosen M, et al. The reliability of a linear analog for evaluating pain. Anaesthesia. 1976;31:1191-1198.
27. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain; the neuropathic pain scale. Neurology. 1997;48:322-338.
28. Miller MD, Ferris DG. Measurement of subjective phenomena in primary care research: the Visual Analogue Scale. Fam Pract Res J. 1993;13:15-24.
29. Melzack R, Toregerson WS. On the language of pain. Anesthesiology. 1971;34:50-59.
30. Wong D, Baker C. Pain in children: comparison of assessment scales. Pediatr Nurs. 1988;14:9-17.
31. Wong D, Baker C. Reference Manual for the Wong-Baker FACES Pain Rating Scale. Tulsa, OK: 1995. Wong and Baker.
32. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975;1:277-299.
33. Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. Cancer. 1982;50:1913-1918.
34. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983;17:197-210.
35. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23:129-138.
36. Cleeland CS. Measurement and prevalence of pain in cancer. Seminar Oncol Nurs. 1985;1:87-92.
37. Breitbart W, Rosenfield B, Passik S, et al. A comparison of pain report and adequacy of analgesic therapy in ambulatory AIDS patients with and without a history of substance abuse. Pain. 1997;72:235-243.
38. Fishman B, Pasternak S, Wallenstien SL, et al. The Memorial Pain Assessment Card: a valid instrument for the evaluation of cancer pain. Cancer. 1987;60:1151-1158.
39. Melzack R. The short-form McGill Pain Questionnaire. Pain. 1987;30:191-197.
40. American Geriatrics Society. The management of chronic pain in older persons: AGS panel on chronic pain in older persons. J Am Geriatr Soc. 1998;46(5):635-651; and Geriatrics. 1998;53(suppl 3):S8-24.
41. American Medical Directors Association. Chronic Pain Management in the Long-Term Care Setting. Columbia, MD: American Medical Directors Association; 1999.

References Section III: Types of Treatments

1. Gallup survey conducted by the Gallup Organization from May 21 to June 9, 1999. Supported by the Arthritis Foundation and Merck & Company, Inc.
2. Whelton A. Renal and related cardiovascular effects of conventional and COX-2-specific NSAIDs and non-NSAID analgesics. Am J Ther. 2000;7(2):63-74.
3. McCormack K, Brune K. Dissociation between the antinociceptive and anti-inflammatory effects of the nonsteroidal anti-inflammatory drugs: a survey of their analgesic efficacy. Drugs. 1991;41:533-547.
4. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature. 1971;234:231-238.
5. Smith JB, Willis AL. Aspirin selectively inhibits prostaglandin production in human platelets. Nat New Biol. 1971;231:235-237.
6. Coyle N, Cherny NI, Portenoy RK. Pharmacologic management of cancer pain In: McGuire DB, Yarbro, CH, Ferrel BR, eds. Cancer Pain Management. 2nd ed. Boston: Jones & Bartlett Publishers; 1995:89-130.
7. Piletta P, Porchet HC, Dayer P. Central analgesic effect of acetaminophen but not of aspirin. Clin Pharmacol Ther. 1991;49:350-354.
8. Miyoshi HR. Systemic nonopioid analgesics. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1667-1681.
9. Kwoh K, Simms RW, Anderson LG, for the American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum. 1996;39(5):713-722.
10. O'Neill GP, Ford-Hutchinson AW. Expression of mRNA for cyclooxygenase-1 and cyclooxygenase-2 in human tissues. FEBS Lett. 1993;330(2):156-160.
11. Griswold DE, Adams JL. Constitutive cyclooxygenase (COX-1) and inducible cyclooxygenase (COX-2): rationale for selective inhibition and progress to date. Med Res Rev. 1996;12;181-206.
12. Pairet M, Engelhardt D. Distinct isoforms (COX-1 and COX-2) of cyclooxygenase: possible physiological and therapeutic implications. Fundam Clin Pharmacol. 1996;10:1-15.
13. Harris RC, McKanna JA, Jacobson HR, et al. Cyclooxygenase-2 is associated with the macula densa of rat kidney and increases with salt restriction. J Clin Invest. 1994;94(6):2504-2510.
14. Komhoff M, Grone HJ, Klein T, et al. Localization of cyclooxygenase-1 and -2 in adult and fetal human kidney: implication for renal function. Am J Physiol. 1997;272(4 pt 2):F460-468.
15. Van Hecken A, Schwartz JI, Depre M, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. J Clin Pharmacol. 2000;40(10):1109-1120.
16. Wight NJ, Gottesdiener K, Garlick NM, et al. Rofecoxib, a COX-2 inhibitor, does not inhibit human gastric mucosal prostaglandin production. Gastroenterology. 2001;120(4):867-873.
17. Vane JR, Botting RM. The history of anti-inflammatory drugs and their mechanism of action. In: Bazan, N, Botting J, Vane J, eds. New Targets in Inflammation: Inhibition of COX-2 or Adhesion Molecules. London: Kluwer Academic Publishers and William Harvey Press; 1996.
18. Matheson AJ, Figgitt DP. Rofecoxib: a review of its use in the management of osteoarthritis, acute pain and rheumatoid arthritis. Drugs. 2001;61(6):833-865.
19. Max MB, Payne R, Edwards WT, et al. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 4th ed. Glenview, IL: American Pain Society; 1999.
20. McCaffery M, Portenoy RK. Overview of three groups of analgesics. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:103-128.
21. McCaffery M, Portenoy RK. Nonopioids: acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs). In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:129-160.

22. Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements. 22nd ed. Montvale, NJ: Medical Economics Company, Inc; 2001.
23. McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999.
24. Jacox AK, Carr DB, Chapman CR, et al. Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; 1992. AHCPR publication 92-0032.
25. Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. JAMA. 1994;272:1845-1850.
26. Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatoxicity with regular intake of alcohol: nalysis of instances of therapeutic misadventure. Hepatology. 1995;22:767-773.
27. Trilisate® Tablets/Liquid (choline magnesium trisalicylate) [package insert]. Stamford, CT: The Purdue Frederick Company; June 9, 2000.
28. Dolobid ® Tablets (diflunisal) [package insert]. West Point, PA: Merck & Co., Inc; July 1998.
29. Motrin® Ibuprofen Tablets, USP [package insert]. Kalamazoo, MI: Pharmacia & Upjohn Company; revised April 2000.
30. EC-Naprosyn® (naproxen) Delayed-Release Tablets, Naprosyn® (naproxen) tablets, Anaprox/Anaprox DS® (naproxen sodium), Naprosyn® (naproxen) suspension [package insert]. Nutley, NJ: Roche Laboratories Inc; revised September 1999.
31. Orudis® (ketoprofen) Capsules, Oruvail® (ketoprofen) Extended-Release Capsules [package insert]. Philadelphia, PA: Wyeth-Ayerst Laboratories; revised November 26, 1997.
32. Ansaid ® (flurbiprofen) Tablets, USP [package insert]. Kalamazoo, MI: Pharmacia & Upjohn Company; revised April 2000.
33. Daypro® (oxaprozin) Caplets [package insert]. Chicago, IL: G. D. Searle & Co; April 29, 1998.
34. Indocin® Capsules, Oral Suspension, and Suppositories (indomethacin) [package insert]. West Point, PA: Merck & Co, Inc; October 1999.
35. Feldene® (piroxicam) Capsules [package insert]. New York, NY: Pfizer Inc; revised June 1999.
36. Mobic® (meloxicam) Tablets [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; and North Chicago, IL: Abbott Laboratories.
37. Arthrotec® (diclofenac potassium and misoprostol) Tablets [package insert]. Chicago, IL: G. D. Searle & Co; revised March 6, 2000.
38. Cataflam® (diclofenac potassium) Immediate-Release Tablets, Voltaren® (diclofenac potassium) Delayed-Release (enteric-coated) Tablets, Voltaren® -XR (diclofenac potassium) Extended-Release Tablets [package insert]. Hanover, NJ: Novartis Pharmaceuticals Corporation; revised May 2000.
39. Toradol® IV/IM (ketorolac tromethamine injection) Toradol ® ORAL (ketorolac tromethamine tablets)[package insert]. Nutley, NJ: Roche Laboratories, Inc; revised March 1999.
40. Vioxx® (rofecoxib) Tablets and Oral suspension) [package insert]. West Point, PA: Merck & Co., Inc; March 2000; revised July 2000.
41. Celebrex ™ (celecoxib) Capsules [package insert]. Chicago, IL: G. D. Searle & Co; and New York, NY: Pfizer, Inc; revised December 1999.
42. Motrin® IB Pain Reliever/Fever Reducer Tablets, Caplets, and Gelcaps (ibuprofen). Fort Washington, PA: McNeil Consumer Healthcare.
43. Motrin® Migraine Pain Caplets (ibuprofen). Fort Washington, PA: McNeil Consumer Healthcare.
44. Regular Strength Tylenol® acetaminophen Tablets; Extra Strength Tylenol® acetaminophen Gelcaps, Geltabs, Caplets, Tablets; Extra Strength Tylenol® acetaminophen Adult Liquid Pain Reliever; Tylenol® acetaminophen Arthritis Pain Extended Release Caplets. Fort Washington, PA: McNeil Consumer Healthcare.
45. Genuine Bayer® Aspirin Tablets, Caplets, and Gelcaps. Morristown, NJ: Bayer Corporation Consumer Care Division.
46. Aspirin Free Excedrin® Caplets and Geltabs (acetaminophen, caffeine). New York, NY: Bristol-Myers Squibb Company.
47. Excedrin® Extra-Strength Analgesic Tablets, Caplets, and Geltabs (acetaminophen, aspirin, caffeine). New York, NY: Bristol-Myers Squibb Company.
48. Excedrin® Migraine Pain Reliever/Pain Reliever Aid Tablets, Caplets, and Geltabs (acetaminophen, aspirin, caffeine). New York, NY: Bristol-Myers Squibb Company.
49. Orudis® KT™ Pain Reliever/Fever Reducer Tablets (ketoprofen) Madison, NJ: Whitehall-Robins Healthcare.
50. Physicians' Desk Reference. 55th ed. Montvale, NJ: Medical Economics Company, Inc; 2001.
51. Lipman AG. Internal analgesic and antipyretic products. In: Handbook of Nonprescription Drugs. Washington DC: American Pharmaceutical Association; 1996:45-74.
52. Manek NJ, Lane NE. Osteoarthritis: current concepts in diagnosis and management. American Academy of Family Physicians. March 15, 2000;61(6)1795-1804. Review.
53. Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ulcers. Br Med J. 1990;300:278-284.
54. Graham DY, Agrawal N, Roth SH. Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. Lancet. 1988;2:1277-1280.
55. Ehsanullah RSB, Page MC, Tildesley G, et al. Prevention of gastroduodenal damage induced by non-steroidal anti-inflammatory drugs: controlled trial of ranitidine. Br Med J. 1988;297;1017-1021.
56. Gay G. Another side effect of NSAIDs [editorial]. JAMA. 1990;264:2677-2678.
57. Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. Lancet. 1999;354(9196):2106-2111.
58. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. JAMA. 1999;282:1921-1928.
59. McKenna F, Borenstein D, Wendt H, et al. Celecoxib versus diclofenac in the management of osteoarthritis of the knee. Scand J Rheumatol. 2001;30(1):11-18.
60. Simon LS, Lanza FL, Lipsky PE, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: efficacy and safety in two placebo-controlled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum. 1998;41:1591-602.
61. Scott LJ, Lamb HM. Rofecoxib. Drugs. 1999;58:499-505.
62. Ehrich EW, Schnitzer TJ, McIlwain H, et al. Effect of specific COX-2 inhibition in osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of rofecoxib. J Rheumatol. 1999;26:2438-2447.
63. Langman MJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA. 1999;282:1929-1933.
64. Greenberg HE, Gottesdiener K, Huntington M, et al. A new cyclooxygenase-2 inhibitor, rofecoxib (VIOXX), did not alter the antiplatelet effects of low-dose aspirin in healthy volunteers. J Clin Pharmacol. 2000;40(12 pt 2):1509-1515.
65. Duggan AW, North RA. Electrophysiology of opioids. Pharmacol Rev. 1983;35:219-281.
66. Benedetti C. Neuroanatomy and biochemistry of antinociception. In: Bonica JJ, Ventafridda V, eds. Advances in Pain Research and Therapy. Vol. 2. New York: Raven Press; 1979:31-44.
67. Stein C. The control of pain in peripheral tissues by opioids. New Engl J Med. 1995;332:1685-1690.
68. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Limbard LE, eds. Goodman & Gillman's the Pharmacologic Basis of Therapeutics. 9th ed. New York: McGraw-Hill, 1996:531-555.
69. Pasero C, Portenoy RK, McCaffery M. Opioid analgesics. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:161-299.
70. Attal N. Chronic neuropathic pain: mechanisms and treatment. Clin J Pain. 2000:16:S118-130.
71. Brookoff D. Chronic pain: 2. The case for opioids. Hospital Practice. Available at: http://www.hosppract.com/issues/2000/09/brook.htm. Accessed June 2001.
72. Carr DB, Jacox AK, Chapman CR, et al., Acute Pain Management in Adults: Operative Procedures Quick Reference Guide for Clinicians No. 1a. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; February 1993. AHCPR publication 92-0019.
73. Jacox A, Carr DB, Payne R, et al. Clinical Practice Guideline: Management of Cancer Pain. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 94-0592.
74. Benjamin, LJ, Dampier CD, Jacox A, et al. Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease. Glenview, IL: American Pain Society; August 1999. APS Clinical Practice Guidelines Series No. 1.
75. Miyoshi HR, Leckband SG. Systemic opioid analgesics. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1682-1709.
76. Roxanol™, Roxanol™ -T, Roxanol 100™ morphine sulfate (immediate release) Oral Solution (concentrate) [package insert]. Columbus, OH: Roxanne Laboratories, Inc; revised February 1999.
77. MSIR® Oral Solution, Oral Solution Concentrate, Immediate-Release Oral Tablets, Immediate-Release Oral Capsules (morphine sulfate) [package insert]. Stamford, CT: The Purdue Frederick Company; June 9, 2000 (2001 PDR pages 2680-2683).
78. MS Contin® Tablets (morphine sulfate controlled release) [package insert]. Stamford, CT: The Purdue Frederick Company; June 9, 2000.
79. Dilaudid® Ampules & Multiple Dose Vials (parenteral), Color Coded Tablets (2, 4 mg), Rectal Suppositories, Non-Sterile Powder (hydromorphone hydrochloride) [package insert]. Mount Olive, NJ: Knoll Pharmaceutical Company; and North Chicago, IL: Abbott Laboratories; revised December 1999.
80. Dilaudid-HP® Injection (hydromorphone hydrochloride) [package insert]. Mount Olive, NJ: Knoll Pharmaceutical Company; revised October 1999.

81. Dilaudid® Oral Liquid and Dilaudid® Tablets (8 mg) (hydromorphone hydrochloride) [package insert]. Mount Olive, NJ: Knoll Pharmaceutical Company; revised October 1999.
82. Duragesic® (Fentanyl Transdermal System) [package insert]. Titusville, NJ: Janssen Pharmaceutica Products, LP; revised January 2000 and February 2001.
83. Percolone® (oxycodone hydrochloride) Tablets [package insert]. Chadds Ford, PA: Endo Pharmaceuticals, Inc; revised September 1999.
84. OxyContin® (oxycodone controlled-release) Tablets [package insert]. Stamford, CT: The Purdue Frederick Company; June 6, 2000.
85. Tylox® Capsules (oxycodone and acetaminophen) [package insert]. Spring House, PA: McNeilLab, Inc; revised June 1997.
86. Percocet® (oxycodone HCl and acetaminophen) Tablets [package insert]. Chadds Ford, PA: Endo Pharmaceuticals, Inc; revised January 2000.
87. Percodan® (oxycodone and aspirin) Tablets [package insert]. Chadds Ford, PA: Endo Pharmaceuticals, Inc; revised November 1999.
88. Demerol® (meperidine hydrochloride) Tablets [package insert]. New York, NY: Sanofi-Synthelabo Inc; September 2000.
89. Vicodin HP® (hydrocodone bitartrate and acetaminophen tablets) [package insert]. Mount Olive, NJ: Knoll Pharmaceutical Company; revised May 2000.
90. Vicodin® (hydrocodone bitartrate and acetaminophen tablets) [package insert]. Mount Olive, NJ: Knoll Pharmaceutical Company; revised May 2000.
91. Vicodin ES® Tablets (hydrocodone bitartrate and acetaminophen tablets) [package insert]. Mount Olive, NJ: Knoll Pharmaceutical Company; revised May 2000.
92. Vicoprofen ® (hydrocodone bitartrate and ibuprofen tablets) [package insert]. Mount Olive, NJ: Knoll Pharmaceutical Company; revised May 2000.
93. Lortab® (2.5/500, 5/500, 7.5/500, 10/500) Tablets and Lortab® Elixer (hydrocodone bitartrate and acetaminophen)[package insert]. Smyrna, GA: UCP Pharma, Inc; no date provided.
94. Codeine Sulfate Tablets [no package insert available]. Columbus, OH: Roxanne Laboratories, Inc.
95. Tylenol® with Codeine (acetaminophen and codeine phosphate) Tablets and Elixir [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; revised July 2000.
96. Kaiko RF, Foley KM, Grabinski PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. Ann Neurol. 1983;13:180-185.
97. Haddox JD, Joranson D, Angarola RT, et al. The Use of Opioids for the Treatment of Chronic Pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Glenview, IL: American Pain Society; 1997. Available at: http://www.ampainsoc.org/advocacy/opioids.htm. Accessed September 2001.
98. Nicholson B. Gabapentin use in neuropathic pain syndromes. Acta Neurol Scand. 2000;101(6):359-71. Review.
99. MacDonald RL, Kelly KM. Mechanisms of action of currently prescribed and newly developed antiepileptic drugs. Epilepsia. 1994;35(suppl 4):S41-50.
100. Weinberger J, Nicklas WJ, Berl S. Mechanism of action of anticonvulsants. Neurology (Minneap). 1976;26:162-173.
101. Covington EC. Anticonvulsants for neuropathic pain and detoxification. Cleve Clin J Med. 1998;65(suppl 1):SI-21-SI-29.
102. Swerdlow M, Cundill JG. Anticonvulsant drugs used in the treatment of lancinating pains: a comparison. Anesthesia. 1981:36:1129-1132.
103. Swerdlow M. Anticonvulsant drugs and chronic pain. Clin Neuropharmacol. 1984;7:51-82.
104. Max MB, Gilron IH. Antidepressants, muscle relaxants, and N-methyl-D-aspartate receptor antagonists. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1710-1726.
105. Rowbotham MC, Peterson KL. Anticonvulsants and local anesthetics. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1727-1735.
106. Galer B. Topical medication. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1736-1741.
107. Portenoy RK, McCaffery M. Adjuvant analgesics. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:300-361.
108. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain. 1997;73(2):123-139.
109. Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. Drugs. 2000;60(5):1029-1052.
110. Carter GT, Galer BS. Advances in the management of neuropathic pain. Phys Med Rehabil Clin N Am. 2001;12(2):447-459.
111. Backonja MM. Painful neuropathies. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:371-387.
112. Backonja MM. Anticonvulsants (antineuropathics) for neuropathic pain syndromes. Clin J Pain. 2000;16(suppl 2):S67-72.
113. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998;280(21):1831-1836.
114. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA. 1998;280(21):1837-1842.
115. Magnus-Miller L, Podolnick P, Mathew NT, et al. Efficacy and safety of gabapentin (Neurontin) in migraine prophylaxis [abstract]. 17th American Pain Society Annual Scientific Meeting; San Diego, CA; November 5-8, 1998.
116. Di Trapani G, Mei D, Marra C, et al. Gabapentin in the prophylaxis of migraine: a double-blind randomized placebo-controlled study. Clin Ter. 2000;151(3):145-148.
117. Watson CP. The treatment of neuropathic pain: antidepressants and opioids.Clin J Pain. 2000;16(suppl 2):S49-55. Review.
118. Bonezzi C, Demartini L. Treatment options in postherpetic neuralgia. Acta Neurol Scand Suppl. 1999;173:25-35; discussion 48-52. Review.
119. Beydoun A. Postherpetic neuralgia: role of gabapentin and other treatment modalities. Epilepsia. 1999;40(suppl 6):S51-56; discussion S73-74.
120. Magnus L. Nonepileptic uses of gabapentin. Epilepsia. 1999;40(suppl 6):S66-72; discussion S73-74.
121. McQuay H, Carroll D, Jadad AR, et al. Anticonvulsant drugs for management of pain: a systemic review. BMJ. 1995;311:1047-1052.
122. McQuay HJ, Tramer M, Nye BA, et al. A systematic review of antidepressants in neuropathic pain. Pain. 1996;68(2-3):217-227.
123. Sumpton JE, Moulin DE. Treatment of neuropathic pain with venlafaxine. Ann Pharmacother. 2001;35(5):557-559.
124. Staab JP, Evans DL. Efficacy of venlafaxine in geriatric depression. Depress Anxiety. 2000;12(suppl 1):63-68.
125. Glassman AH, Bigger JT. Cardiovascular effects of therapeutic doses of tricyclic antidepressants. Arch General Psychiatry. 1981:38:815-820.
126. Rowbotham MC, Reisner-Kelly LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. Neurology. 1991;41:1024-1028.
127. Kastrup J, Petersen P, Dejgard A, et al. Intravenous lidocaine infusion: a new treatment for chronic painful diabetic neuropathy. Pain. 1987;28:69-75.
128. Backonja M, Gombar K. Response of central pain syndromes to intravenous lidocaine. J Pain Symptom Manage. 1992;7:172-178.
129. Dejgard A. Petersen P, Kastrup J. Mexiletine for treatment of chronic painful diabetic neuropathy. Lancet. 1988:1:9-11.
130. Dunlop R, Davies RJ, Hockley F, et al. Letter to the editor. Lancet. 1989;1:420-421.
131. Neurontin® (gabapentin) Capsules, Neurontin® (gabapentin) Tablets; Neurontin® (gabapentin) Oral Solution [package insert]. Morris Plains, NJ: Parke-Davis, Division of Warner-Lambert Division, a Pfizer Company; revised February 1999 and November 199 (Pfizer web site).
132. Tegretol® (carbamazepine) Chewable Tablets, Tablets, Suspension; Tegretol-XR (carbamazepine extended-release tablets) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; revised June 2000.
133. Depakote® Tablets (divalproex sodium delayed-release tablets) [package insert]. North Chicago, IL: Abbott Laboratories; revised June 2000.
134. Depakote® ER (divalproex sodium extended-release tablets) [package insert]. North Chicago, IL: Abbott Laboratories; revised August 2000.
135. Dilantin® Kapseals® (extended phenytoin sodium capsules, USP) [package insert]. Morris Plains, NJ: Parke-Davis, Division of Warner-Lambert Division, a Pfizer Company; revised May 1999.
136. Dilantin-125® (Phenytoin Oral Suspension, USP) [package insert]. Morris Plains, NJ: Parke-Davis, Division of Warner Lambert Division, a Pfizer Company; revised May 1999.
137. Elavil® (amitriptyline HCl) Tablets and Injection [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; revised August 1998.
138. Nortriptyline HCl capsules [no package insert available]. Broomfield, CT: Geneva Pharmaceuticals.
139. Lidoderm® (lidocaine patch 5%) [package insert]. Chadds Ford, PA: Endo Pharmaceuticals; July 1999.
140. EMLA® Anesthetic Disk (lidocaine 2.5% and prilocaine 2.5% cream) Topical Adhesive System, EMLA® Cream (lidocaine 2.5% and prilocaine 2.5%) [package insert]. Wilmington, DE: AstraZeneca LP; revised July 1999.
141. Sensorcaine® (bupivacaine HCl Injection, USP); Sensorcaine®-MPF (bupivacaine HCl Injection, USP); Sensorcaine® with Epinephrine (bupivacaine HCl and epinephrine Injection, USP); Sensorcaine®-MPF with Epinephrine (bupivacaine HCl and epinephrine Injection, USP) [package insert]. Wilmington, DE: AstraZeneca LP; revised March 1997.
142. Xylocaine® (lidocaine HCl Injection, USP); Xylocaine® (lidocaine HCl and epinephrine Injection, USP) [package insert]. Wilmington, DE: AstraZeneca LP; revised April 2000.
143. Chadda VS, Mathur MS. Double blind study of the effects of diphenylhydantoin sodium on diabetic neuropathy. J Assoc Physicians India. 1978;26:403-406.

144. Lockman LA, Hunningshake DB, Krivit W, et al. Relief of pain of Fabry's disease by diphenylhydantoin. Neurology. 1973:23:871-875.
145. Saudek CD, Werns S, Reidenber MM. Phenytoin in the treatment of diabetic symmetrical polyneuropathy. Clin Pharmacol Ther. 1977;22:196-199.
146. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998;280(21):1831-1836.
147. Backonja MM. Gabapentin monotherapy for the symptomatic treatment of painful neuropathy: a multicenter, double-blind, placebo-controlled trial in patients with diabetes mellitus. Epilepsia. 1999;40(suppl 6):S57-59; discussion S73-74.
148. Merren MD. Gabapentin for treatment of pain and tremor: a large case series. South Med J. 1998;91(8):739-744.
149. Weber WE. Ned Tijdschr Geneeskd [in Dutch]. 2001;145(17):813-817.
150. Block F. Gabapentin therapy for pain. Nervenarzt. 2001;72(2):69-77.
151. Sawynok J, Esser MJ, Reid AR. Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. J Psychiatry Neurosci. 2001;26(1):21-29.
152. Yaksh TL. Direct evidence that spinal serotonin and noradrenaline terminals mediate the spinal antinociceptive effects of morphine in the periaqueductal gray. Brain Res. 1979;160:180-185.
153. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. Annu Rev Neurosci. 1984;7:309-338.
154. Besson JM, Chaouch A. Peripheral and spinal mechanism of nociception. Physiol Rev. 1987;67:67-186.
155. O'Malley PG, Jackson JL, Santoro J, et al. Antidepressant therapy for unexplained symptoms and symptom syndromes. J Fam Pract. 1999;48(12):980-990. Review.
156. Kishore-Kuman R, Max MB, Schafer SC, et al. Desipramine relieves postherpetic neuralgia. Clin Pharmacol Ther. 1990;47:305-312.
157. Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology. 1987;37:589-596.
158. Watson CP, Evan RJ, Reed K, et al. Amitriptyline versus placebo in postherpetic neuralgia. Neurology. 1982;32:671-673.
159. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med. 1992; 326:1250-1256.
160. Collins SL, Moore RA, McQuay HJ, et al. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. J Pain Symptom Manage. 2000;20(6):449-458.
161. Morello CM, Leckband SG, Stoner CP, et al. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med. 1999;159(16):1931-1937.
162. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. J Psychiatr Neurosci. 2001;26(1):30-36. Review.
163. Davies PS, Reisner-Keller LA, Rowbothan MC. Randomized, double-blind comparison of fluoxetine, desipramine, and amitriptyline in postherpetic neuralgia [abstract]. Abstracts: 8th World Congress on Pain. Seattle, WA: IASP Press;1996.
164. Max MB. Treatment of post-herpetic neuralgia: antidepressants. Ann Neurol. 1994;(suppl 35):S50-53. Review.
165. Sindrup SH, Gram LF, Brosen K, et al. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. Pain. 1990;42:135-144.
166. Fishbain D. Evidence-based data on pain relief with antidepressants. Ann Med. 2000;32(5):305-16. Review.
167. Covino BG. Local anesthetics. In: Ferrante FM, VadeBoncourer TR, eds. Postoperative Pain Management. New York: Churchill Livingstone; 1993:211-253.
168. Woolf CJ, Wiesenfeld-Hallis Z. The systemic administration of local anesthetic produces a selective depression of C-afferent evoked activity in the spinal cord. Pain. 1985;23:361-374.
169. Chabal C, Russell LC, Burchiel KJ. The effect of intravenous lidocaine, tocainide, and mexiletine on spontaneously active fibers originating in rat sciatic neuromas. Pain. 1989;38:333-338.
170. AstraZeneca. Pain control & anesthesia, AstraZeneca products. Available at: http://www.astrazeneca.com/Products/Pain_control_and_anaesthesia_products.htm#. Accessed September 2001.
171. Hallen B, Carlsson P, Uppfeldt A. Clinical study of lignocaine-prilocaine cream to relieve the pain of venipuncture. Br J Anaesth. 1985;57(3):326-328.
172. Hallen B, Olsson Gl, Uppfeldt A. Pain free venipuncture. Anesthesia. 1984;39:969-972.
173. Vaghadia H, al Ahdal OA, Nevin K. EMLA patch for intravenous cannulation in adult surgical outpatients. Can J Anaesth. 1997;44:798-802.
174. Sharma SK, Gajraj NM, Sidawi JE, et al. EMLA cream effectively reduces the pain of spinal needle insertion. Reg Anesth. 1996;21:561-564.
175. Gupta AK, Sibbald RG. Eutectic lidocaine/prilocaine 5% cream and patch may provide satisfactory analgesia for excisional biopsy or curettage with electrosurgery of cutaneous lesions. J Am Acad Dermatol. 1996;35:419-423.
176. deWaardvanderSpek FB, Mulder PG, Oranje AP. Prilocaine/lidocaine patch as a local premedication for skin biopsy in children. J Am Acad Dermatol. 1997;37:418-421.
177. Argoff CE. New analgesics for neuropathic pain: the lidocaine patch. Clin J Pain 2000;16(suppl 2):S62-66.
178. Rowbotham MC, Davies PS, Verkempinck C, et al. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. Pain. 1996;65(1):39-44.
179. Galer BS, Rowbotham MC, Perander J, et al. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain. 1999;80(3):533-538.
180. Rowbotham MC, Davies PC, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. Ann Neurol. 1995;37:246-253.
181. Devers A, Galer BS. Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. Clin J Pain. 2000;16(3):205-208.
182. Ray A. Physiology and management of acute pain. 2001 Hospital Consultants Meeting; New Orleans, LA; May 18-21, 2001.
183. Cossman M, Wilsman KM. Effect and side effects of tramadol: an open phase IV study with 7,198 patients. Tehrapiewoche. 1987;37:3475-3495.
184. Preston KL, Jasinski DR, Testa M. Abuse potential and pharmacological comparison of tramadol and morphine. Drug Alcohol Depend. 1991;27:7-17.
185. Rauck RL, Ruoff GE, McMillen JI. Comparison of tramadol and acetaminophen with codeine for long-term pain management in elderly patients. Curr Ther Res. 1994;55:1417-1431.
186. Raffa RB, Friderichs E, Reimann W, et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an atypical opioid analgesic. J Pharmacol Exp Ther. 1992;260:275-285.
187. Ettinger AB, Portenoy RK. The use of corticosteroids in the treatment of symptoms associated with cancer. J Pain Symptom Manage. 1988;3:99-103.
188. Decadron® Elixir (dexamethasone) [package insert]. West Point, PA: Merck & Co, Inc; February 1997.
189. Decadron® Tablets (dexamethasone) [package insert]. West Point, PA: Merck & Co., Inc; February 1997.
190. Decadron® Phosphate Injection (dexamethasone sodium phosphate) [package insert]. West Point, PA: Merck & Co, Inc; July 1999.
191. Methylprednisolone tablets [no package insert available]. Corona, CA: Watson Laboratories.
192. Ultram® (tramadol hydrochloride tablets) [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; December 1999.
193. Zomig® (zolmitriptan) Tablets [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; revised May 2000.
194. Maxalt® (rizatriptan benzoate) Tablets, Maxalt-MLT® (rizatriptan benzoate) Orally Disintegrating Tablets [package inserts]. West Point, PA: Merck & Co, Inc; August 1999 and July 2000 (Merck web site).
195. Imitrex® (sumatriptan succinate) Injection [package insert]. Research Triangle Park, NC: Glaxo Wellcome, Inc; September 1999.
196. Imitrex® (sumatriptan) Nasal Spray [package insert]. Research Triangle Park, NC: Glaxo Wellcome, Inc; September 1999.
197. Imitrex® (sumatriptan succinate) Tablets [package insert]. Research Triangle Park, NC: Glaxo Wellcome Inc; September 1999.
198. Inderal® (propranolol hydrochloride) Tablets, Inderal (propranolol hydrochloride) Injectable [package insert]. Philadelphia, PA: Wyeth-Ayerst Laboratories; revised March 17, 1999.
199. Inderal® LA (propranolol hydrochloride) Long-Acting Capsules [package insert]. Philadelphia, PA: Wyeth-Ayerst Laboratories; revised March 17, 1999.
200. Baclofen tablets [no package insert available]. Corona, CA: Watson Laboratories, Inc.
201. Institute for Clinical Systems Improvement (ICSI) Work Group. Assessment and Management of Acute Pain. ICSI health care guideline. September 2000.
202. Payne R, Chandler SW, Einhaus E. Guidelines for the clinical use of transdermal fentanyl. Anticancer Drugs. 1995;6:50-53.
203. Ahmedzai S, Brooks D, for the TTS-Fentanyl Comparative Trial Group. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. J Pain Symptom Manage. 1997;13:254-261.
204. Payne R, Mathias SD, Pasta DJ, et al. Quality of life and cancer pain: satisfaction and side effects with transdermal fentanyl versus oral morphine. J Clin Oncol. 1998;16:1588-1593.
205. Allen L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating non-cancer pain. BMJ. 2001;322:1-7.
206. Barash PG, Cullen BF, Stoelting RK, eds. Handbook of Clinical Anesthesia. 3rd ed. Philadelphia, PA: Lippincott-Raven; 1997.
207. Pasero C, McCaffery M. Procedural pain management. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:362-398.
208. White PF. Patient-controlled analgesia, II: comparative studies and alternative routes of administration. In: Stanley TH, Ashburn Ma, Fine PG, eds. Anesthesiology and Pain Management. Dordrecht, Netherlands: Kluwer Academic Publishers; 1991:245-248.

209. American Society of Addiction Medicine. Definitions Related to the Use of Opioids for the Treatment of Pain. Consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. February 2001. Available at: http://www.asam.org. Accessed June 2001.
210. Bonica JJ, Bendetti C. Management of cancer pain. In: Moosa AR, Robson MC, Schimpff SC, eds. Comprehensive Textbook of Oncology. Baltimore, MD: Williams & Wilkins; 1985:443-477.
211. Weissman DE, Burchman SL, Dinndorf PA, et al. Handbook of Cancer Pain Management. 2nd ed. Milwaukee, WI: Wisconsin Cancer Pain Initiative; 1990.
212. Wallace K. The pathophysiology of pain. Crit Care Nurs Q. 1992;15(2):1-13.
213. Dunajcik L. Chronic nonmalignant pain. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:467-521.
214. Fordyce WE. Operant or contingency therapies. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1745-1750.
215. Chapman CR. Section C. Psychological techniques introduction. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1743-1744.
216. Arena JG, Blanchard EB. Biofeedback therapy for chronic pain disorders. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1759-1767.
217. Barber J. Hypnosis. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1768-1778.
218. Syrjala KL. Relaxation and imagery techniques. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1779-1788.
219. Gottlieb H. Medication nonadherence: finding solutions to a costly medical problem. Drug Benefit Trends. 2000;12:57-62.
220. Heavner JE, Shi B, Diede J, et al. Acetaminophen (paracetamol) use and blood concentrations in pain patients. Pain Dig. 1996;6:215-218.
221. Burney KD, Krishnan K, Ruff MT, et al. Adherence to single daily dose of aspirin in a chemoprevention trial: an evaluation of self-report and microelectronic monitoring. Arch Fam Med. 1996;5:297-300.
222. Chapman CR. Compliance with pain medication: a hidden problem? APS Bulletin. 1996;6(6):11.
223. McCaffery M Pasero C. Practical nondrug approaches to pain. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:399-427.
224. Willick SE, Herring SA, Press JM. Basic concepts in biomechanics and musculoskeletal rehabilitation. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1815-1831.
225. Ramsay DJ, Bowman MA, Greenman PE, et al, for the National Institutes of Health (NIH) Consensus Development Panel. Acupuncture. NIH Consensus Statement Online. November 3-5 1997;15(5):1-34. Available at: http://odp.od.nih.gov/consensus/cons/107/107_statement.htm#8_Consen. Accessed September 2001.
226. Osiri M, Welch V, Brosseau L, et al. Transcutaneous electrical nerve stimulation for knee osteoarthritis. Cochrane Database Syst Rev. 2000;(4):CD002823. Review.
227. Yurtkuran M, Kocagil T. TENS, electroacupuncture and ice massage: comparison of treatment for osteoarthritis of the knee. Am J Acupunct. 1999;27(3-4):133-140.
228. Offenbacher M, Stucki G. Physical therapy in the treatment of fibromyalgia. Scand J Rheumatol Suppl. 2000;113:78-85. Review.
229. Patil PG, Campbell JN. Lesions of primary afferent and sympathetic efferents as treatments for pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:2011-2022.

References Section IV: Management of Acute Pain and Chronic Noncancer Pain

1. Jacox AK, Carr DB, Chapman CR, et al. Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; 1992. AHCPR publication 92-0032.
2. Wilson PR, Caplan RA, Connis RT, et al, of the American Society of Anesthesiologists, Task Force on Pain Management, Chronic Pain Section. Practice guidelines for chronic pain management. Anesthesiology. 1997;86(4):995-1004.
3. Dahl JB, Rosenberg J, Dirkes WE, et al. Prevention of postoperative pain by balanced analgesia. Br J Anaesth. 1990;64:518-520.
4. Dahl JB, Kehlet Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. Br J Anaesth. 1991;66:703-712.
5. Kehlet H, Dahl JB. The value of "multimodal" or "balanced" analgesia in postoperative pain treatment. Anesth Analg. 1993;77:1048-1056.
6. McCaffery M, Portenoy RK. Overview of three groups of analgesics. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999a:103-128.
7. Kehlet H. Postoperative pain relief: what is the issue? Br J Anaesth. 1994;72:374-378.
8. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997;78:606-617.
9. Kehlet H. Acute pain control and accelerated postoperative surgical recovery. Surg Clin North Am. 1999;29(2):431-443.
10. Reuben SS, Connelly NR. Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth Analg. 2000;91(5):1221-1225.
11. Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after postoperative lumbar epidural blockade. Pain. 1988;33:297-301.
12. Jahangiri M, Jayatunga AP, Bradley JW, et al. Prevention of phantom pain after major lower limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine. Ann R Coll Surg Engl. 1994;76(5):324-326.
13. Nikolajsen L, Ilkjaer S, Christensen JH, et al. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet. 1997;350:1353-1357.
14. Lambert AW, Dashfield AK, Cosgrove C, et al. Randomized prospective study comparing preoperative epidural and intraoperative perineural analgesia for the prevention of postoperative stump and phantom limb pain following major amputation.Reg Anesth Pain Med. 2001;26(4):316-321.
15. Kehlet H. Preemptive analgesia in postoperative pain: the second round will need a change in tactics. Plenary Session, APS 20th Annual Scientific Meeting, April 26, 2001. Available at: http://www.ampainsoc.org/meeting/annual_01/friday.htm. Accessed September 2001.
16. Katz J. Phantom limb pain. Lancet. 1997;350:1338-1339.
17. Max MB, Payne R, Edwards WT, et al. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 4th ed. Glenview, IL: American Pain Society; 1999.
18. Carr DB, Jacox AK, Chapman CR, et al. Acute Pain Management in Adults: Operative Procedures Quick Reference Guide for Clinicians No. 1a. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; February 1993. AHCPR publication 92-0019.
19. Ready BL, Ashburn M, Caplan R, et al, of the American Society of Anesthesiologists, Task Force on Pain Management, Acute Pain Section. Practice guidelines for acute pain management in the perioperative setting. Anesthesiology. 1995;82(4):1071-1078.
20. Hawkins JL, Arens JF, Bucklin BA, et al, of the American Society of Anesthesiologists Task Force on Obstetrical Anesthesia. Practice guidelines for obstetrical anesthesia. Anesthesiology. 1999;90(2):600-611.
21. Institute for Clinical Systems Improvement (ICSI) Work Group. Assessment and Management of Acute Pain. ICSI health care guideline. September 2000.
22. Ashburn MA, Ready LB. Postoperative pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:765-779.
23. Edwards WT. Postrauma pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:780-787.
24. Patterson DR, Sharar SR. Burn pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:780-787.
25. Moskal MJ, Matsen FA. Orthopedic management of pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1807-1814.
26. Pasero C, McCaffery M. Procedural pain management. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:362-398.
27. McCaffery M, Pasero C. Practical nondrug approaches to pain. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:399-427.
28. Marcus DA. Treatment of nonmalignant chronic pain. Am Fam Physician. March 1, 2000;61(5):1331-1338, 1345-1346. Review.
29. Dunajcik L. Chronic nonmalignant pain. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:467-521.
30. Covington EC. Multidisciplinary pain management organization and outcomes [syllabus]. Personal communication, 1999.
31. Flor H, Fyrich T, Turk DC. Efficacy of multidisciplinary pain treatment centers: a meta-analytic review. Pain. 1992;49:221-230.
32. Turk DC, Okifuji A. Efficacy of multidisciplinary pain centres: an antidote to anecdotes. Baillieres Clin Anaesthesiol. 1998;12:103–119.
33. Commission on Accreditation of Rehabilitation Facilities. 1998 Standards Manual for and Interpretive Guidelines for Medical Rehabilitation. Tucson, AZ: Commission on Accreditation of Rehabilitation Facilities; 1998.

34. Commission on Accreditation of Rehabilitation Facilities. 1999 Standards Manual for and Interpretive Guidelines for Medical Rehabilitation. Tucson, AZ: Commission on Accreditation of Rehabilitation Facilities; 1999.
35. Lipchik GL, Milles K, Covington EC. The effects of multidisciplinary pain management treatment on locus of control and pain beliefs in chronic non-terminal pain. Clin J Pain. 1993;9(1):49-57.
36. The Cleveland Clinic Foundation, Rehabilitation Institute. Pain management. Available at: http://www.clevelandclinic.org/rehab/rb02/02-01b.htm. Accessed September 2001.
37. The Cleveland Clinic Foundation, Rehabilitation Institute. Special services. Available at: http://www.clevelandclinic.org/rehab/rb02/02-01.htm. Accessed September 2001.
38. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA. 1998;280(21):1837-1842.
39. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998;280(21):1831-1836.
40. Covington EC. Opioid maintenance in chronic non-malignant pain [syllabus]. Personal communication, September 30, 1999.
41. Haddox JD, Joranson D, Angarola RT, et al. The Use of Opioids for the Treatment of Chronic Pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Glenview, IL: American Pain Society; 1997. Available at: http://www.ampainsoc.org/advocacy/opioids.htm. Accessed September 2001.
42. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage. 1992;7(2):69-77.
43. Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. J Pain Symptom Manage. 1993;8(5):279-88. Review.
44. Winkelmuller M, Winkelmuller W. Long-term effects of continuous intrathecal opioid treatment in chronic pain of nonmalignant etiology. J Neurosurg. 1996;85(3):458-467.
45. Sjogren P, Thunedborg LP, Christrup L, et al. Is development of hyperalgesia, allodynia and myoclonus related to morphine metabolism during long-term administration? Six case histories. Acta Anaesthesiol Scand. 1998;42(9):1070-1075.
46. Li X, Angst MS, Clark JD. A murine model of opioid-induced hyperalgesia. Brain Res Mol Brain Res. 2001;86(1-2):56-62.
47. Li X, Angst MS, Clark JD. Opioid-induced hyperalgesia and incisional pain. Anesth Analg. 2001;93(1):204-209.
48. Portenoy RK. Opioid therapy for chronic nonmalignant pain: current status. In: Fields HL, Liebeskind JC, eds. Progress in Pain Research and Management. Vol. 1. Pharmacologic Approaches to the Treatment of Chronic Pain: New Concepts and Critical Issues. Seattle, WA: IASP Press; 1994:274-275.
49. Hochberg MC, Altman RD, Brandt KD, et al, of the Board of Directors, American College of Rheumatology. Guidelines for the medical management of osteoarthritis, part I: osteoarthritis of the hip. Arthritis Rheum. 1995;38:1535-1540.
50. Hochberg MC, Altman RD, Brandt KD, et al, of the Board of Directors, American College of Rheumatology. Guidelines for the medical management of osteoarthritis, part II: osteoarthritis of the knee. Rheum. 1995;38:1541-1546.
51. Manek NJ, Lane NE. Osteoarthritis: current concepts in diagnosis and management. Am Fam Physician. March 15, 2000;61(6):1795-1804. Review.
52. Kwoh K, Simms RW, Anderson LG, of the American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum. 1996;39(5):713-722.
53. Gardner GC, Gilliland BC. Arthritis and periarthritic disorders. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:503-521.
54. Benjamin, LJ, Dampier CD, Jacox A, et al. Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease. Glenview, IL: American Pain Society; August 1999. APS Clinical Practice Guidelines Series No. 1.
55. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Questions and answers about arthritis pain. Available at: http://www.nih.gov/niams/healthinfo/arthpain.htm. Accessed February 2001.
56. McCaffery M. Selected pain problems. In: McCaffery M, Pasero C, eds. Pain Clinical Manual. 2nd ed. St. Louis, MO: Mosby Inc; 1999:522-607.
57. Institute for Clinical Systems Improvement (ICSI) Work Group. Diagnosis and Treatment of Adult Degenerative Joint Disease (DJD) of the Knee. ICSI health care guideline. November 2000.
58. Institute for Clinical Systems Improvement (ICSI) Work Group. Adult Low Back Pain. ICSI health care guideline. November 1999.
59. Jacox A, Carr DB, Payne R, et al. Clinical Practice Guideline: Management of Cancer Pain. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 94-0592.
60. Bigos S, Bowyer O, Braen G, et al. Acute Low Back Problems in Adults. Guideline No. 14. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 95-0642.
61. Bigos S, Bowyer O, Braen G, et al. Acute Low Back Problems in Adults: Assessment and Treatment Quick Reference Guide No. 14. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 95-0643.
62. Jacox A, Carr DB, Payne R, et al. Management of Cancer Pain: Adults Quick Reference Guide No. 9. Rockville, MD: U.S. Department of Human and Health Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 94-0593.
63. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Questions and answers about fibromyalgia. Available at: http://www.nih.gov/niams/healthinfo/fibrofs.htm. Accessed February 2001.
64. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum. 1990;34(1):15-21.
65. National Fibromyalgia Partnership, Inc. An overview of the fundamental features of fibromyalgia syndrome. FMS monograph, 1999. Available at: http://www.fmpartnership.org/engmonog.htm. Accessed October 2001.
66. Preboth M. Management of pain in sickle cell disease. Am Fam Physician. March 1, 2000;61(5):1544, 1549-1550.
67. National Institute of Neurological Disorders and Stroke. Peripheral neuropathy information page. Available at: http://www.ninds.gov/health_and_medical/disorders/peripheral neuropathy_doc.html. Accessed September 2000.
68. Backonja MM. Painful neuropathies. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:371-387.
69. Carter GT, Galer BS. Advances in the management of neuropathic pain. Phys Med Rehabil Clin N Am. 2001;12(2):447-459.
70. Backonja MM. Anticonvulsants (antineuropathics) for neuropathic pain syndromes. Clin J Pain. 2000;16(suppl 2):S67-72.
71. Morey SS. Guidelines on migraine: part 2. General principles of drug therapy. Am Fam Physician. October 15, 2000;62(8):1915-1917.
72. Morey SS. Guidelines on migraine: part 3. Recommendations for individual drugs. Am Fam Physician. November 1, 2000;62(9):2145-2148, 2151
73. Morey SS. Guidelines on migraine: part 4. General principles of preventive therapy. Am Fam Physician. November 15, 2000;62(10):2359-2360, 2363.
74. Morey SS. Guidelines on migraine: part 5. Recommendations for specific prophylactic drugs. Am Fam Physician. December 1, 2000;62(11):2535-2539. Review.
75. Silberstein SD, for the US Headache Consortium. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). American Academy of Neurology. Neurology. 2000;55:754-763.
76. McCrory DC, Matchar DB, Gray RN, et al. Evidence-based guidelines for migraine headache: overview of program description and methodology. The U.S. Headache Consortium, American Academy of Neurology. April 2000. Available at: http://www.aan.com/public/practiceguidelines/01.pdf. Accessed October 2001.
77. Ramadan NM, Silberstein SD, Freitag FG, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. The U.S. Headache Consortium, American Academy of Neurology. April 2000. Available at: http://www.aan.com/public/practiceguidelines/headache_gl.htm. Accessed October 2001.
78. Matchar DB, Young WB, Rosenberg JH, et al. Evidence based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. The U.S. Headache Consortium, American Academy of Neurology. April 2000. Available at: http://www.aan.com/public/practiceguidelines/headache_gl.htm. Accessed October 2001.
79. Welch KMA. Headache. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:867-895.
80. Institute for Clinical Systems Improvement (ICSI) Work Group. Migraine Headache. ICSI health care guideline. May 2000.
81. Lohmander LS, Dalen N, Englund G, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. Hyaluronan Multicentre Trial Group. Ann Rheum Dis. 1996;55:424-431.
82. Adams ME, Atkinson MH, Lussier AJ, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis Cartilage. 1995;3:213-225.
83. Buckley PF. Regional anesthesia with local anesthetics. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1893-1952.
84. Erjavec M. Epidural steroids for low back pain. In: Loeser JD, Butler SH, Chapman CR, et al, eds. Bonica's Management of Pain. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2001:1557-1562.

85. Buckwalter JA, Lohmander S. Operative treatment of osteoarthritis. Current practice and future development. J Bone Joint Surg Am. 1994;76:1405-1418.
86. Lewis C. What to do when your back is in pain. U.S. Food and Drug Administration web site. Available at: http://www.fda.gov/fdac/features/1998/298_back.html. Accessed February 2001.
87. Bennett RM. The fibromyalgia syndrome: myofascial pain and the chronic fatigue syndrome. In: Kelly WN, Harris ED, Ruddy SE, et al, eds. Textbook of Rheumatology. Vol 1. 4th ed. Philadelphia, PA: WB Saunders; 1993:471-479.
88. Campbell, JK, Penzine DB, Wall EM. Evidence-based guidelines for migraine headache: Behavioral and physical treatments. The U.S. Headache Consortium, American Academy of Neurology. April 2000. Available at: http://www.aan.com/public/practiceguidelines/headache_gl.htm. Accessed October 2001.
89. Poncelet AN. An algorithm for the evaluation of peripheral neuropathy. Am Fam Physician. February 15, 1998;57(4):755-764.
90. Osiri M, Welch V, Brosseau L, et al. Transcutaneous electrical nerve stimulation for knee osteoarthritis. Cochrane Database Syst Rev. 2000;(4):CD002823. Review.
91. Offenbacher M, Stucki G. Physical therapy in the treatment of fibromyalgia. Scand J Rheumatol Suppl. 2000;113:78-85. Review.

References Section V: Strategies to Improve Pain Management

1. Jacox AK, Carr DB, Chapman CR, et al. Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; 1992. AHCPR publication 92-0032.
2. Carr DB, Jacox AK, Chapman CR, et al. Acute Pain Management in Adults: Operative Procedures Quick Reference Guide for Clinicians No. 1a. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; February 1993. AHCPR publication 92-0019.
3. Ready BL, Ashburn M, Caplan R, et al, of the American Society of Anesthesiologists Task Force on Pain Management, Acute Pain Section. Practice guidelines for acute pain management in the perioperative setting. Anesthesiology. 1995;82(4):1071-1078.
4. Gross JB, Bailey PL, Caplan RA, et al, of the American Society of AnesthesiologistsTask Force on Sedation and Analgesia by Non-Anesthesiologists . Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology. 1996;84(2):459-471.
5. Wilson PR, Caplan RA, Connis RT, et al, of the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. Practice guidelines for chronic pain management. Anesthesiology. 1997;86(4):995-1004.
6. Young D. Acute Pain Management. Iowa City, IA: University of Iowa Gerontological Nursing Interventions Center; April 6, 1999. Titler MG, ed. Research-based protocol No. 1999.
7. American Geriatrics Society. The management of chronic pain in older persons: AGS panel on chronic pain in older persons. J Am Geriatr Soc. 1998;46(5):635-651; and Geriatrics. 1998;53(suppl 3):S8-24.
8. Max MB, Payne R, Edwards WT, et al. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 4th ed. Glenview, IL: American Pain Society; 1999.
9. American Medical Directors Association. Chronic Pain Management in the Long-Term Care Setting. Columbia, MD: American Medical Directors Association; 1999.
10. Marcus DA. Treatment of nonmalignant chronic pain. Am Fam Physician. March 1, 2000;61(5):1331-1338, 1345-1346. Review.
11. Institute for Clinical Systems Improvement (ICSI) Work Group. Assessment and Management of Acute Pain. ICSI health care guideline. September 2000.
12. Jacox A, Carr DB, Payne R, et al. Clinical Practice Guideline: Management of Cancer Pain. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 94-0592.
13. Bigos S, Bowyer O, Braen G, et al. Acute Low Back Problems in Adults. Guideline No. 14. Rockville, MD: U.S. Department of Health and Human Services, Agency for Health Care Policy and Research; 1994. AHCPR publication 95-0642.
14. Hochberg MC, Altman RD, Brandt KD, et al, of the Board of Directors, American College of Rheumatology. Guidelines for the medical management of osteoarthritis, part I: osteoarthritis of the hip. Arthritis Rheum. 1995;38:1535-1540.
15. Hochberg MC, Altman RD, Brandt KD, et al, of the Board of Directors, American College of Rheumatology. Guidelines for the medical management of osteoarthritis: part II: osteoarthritis of the knee. Arthritis Rheum. 1995;38:1541-1546.
16. Kwoh K, Simms RW, Anderson LG, of the American College of Rheumatology (ACR) Ad Hoc Committee on Clinical Guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum. 1996;39(5):713-722.
17. Ferrante M, Bedder M, Caplan RA, et al, of the American Society of Anesthesiologists Task Force on Pain Management, Cancer Pain Section. Practice guidelines for cancer pain management. Anesthesiology. 1996;84:1243-1257.
18. Ramsay DJ, Bowman MA, Greenman PE, et al, for the National Institutes of Health (NIH) Consensus Development Panel. Acupuncture. NIH Consensus Statement Online. November 3-5 1997;15(5):1-34. Available at:http://odp.od.nih.gov/consensus/cons/107/107_statement.htm#8_Consens. Accessed September 2001.
19. Institute for Clinical Systems Improvement (ICSI) Work Group. Adult Low Back Pain. ICSI health care guideline. November 1999.
20. Hawkins JL, Arens JF, Bucklin BA, et al, of the American Society of Anesthesiologists Task Force on Obstetrical Anesthesia. Practice guidelines for obstetrical anesthesia. Anesthesiology. 1999;90(2):600-611.
21. Backer D, Brill D, Donogoe K, et al, of the Society of Nuclear Medicine, Inc. Guideline Task Force. Procedure Guideline for Bone Pain Treatment. Reston, VA: Society of Nuclear Medicine; February 1999. 26 pages. Society of Nuclear Medicine Procedure Guidelines, version 2.0.
22. Poss B, Clark CR, Johnson R, et al, of the American Academy of Orthopaedic Surgeons (AAOS) Task Force on Clinical Algorithms, AAOS Committee on Clinical Policies. Clinical Guideline on Hip Pain. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1999.
23. Rosenberg A, Harwin SF, Sculco T, et al, of the American Academy of Orthopaedic Surgeons Task Force on Clinical Algorithms. Clinical Guideline on Knee Pain. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1999.
24. Berger R, Cooney W, Simmons B, et al, of the American Academy of Orthopaedic Surgeons (AAOS) Task Force on Clinical Algorithms, AAOS Committee on Clinical Policies. Clinical Guideline on Wrist Pain. Rosemont, IL: American Academy of Orthopaedic Surgeons; 1999.
25. Benjamin, LJ, Dampier CD, Jacox A, et al. Guideline for the Management of Acute and Chronic Pain in Sickle Cell Disease. Glenview, IL: American Pain Society; August 1999. APS Clinical Practice Guidelines Series No. 1.
26. McCrory DC, Matchar DB, Gray RN, et al. Evidence-based guidelines for migraine headache: overview of program description and methodology. The U.S. Headache Consortium, American Academy of Neurology. April 2000. Available at: http://www.aan.com/public/practiceguidelines/01.pdf. Accessed October 2001.
27. Campbell, JK, Penzine DB, Wall EM. Evidence-based guidelines for migraine headache: Behavioral and physical treatments. The U.S. Headache Consortium, American Academy of Neurology. April 2000. Available at: http://www.aan.com/public/practiceguidelines/headache_gl.htm. Accessed October 2001.
28. Silberstein SD, for the US Headache Consortium. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). American Academy of Neurology. Neurology. 2000;55:754-763.
29. Frishberg BM, Rosenberg JH, Matchar DB, et al. Evidence-based guidelines for migraine headache: neuroimaging in patients with nonacute headache. The U.S. Headache Consortium, American Academy of Neurology. April 2000. Available at: http://www.aan.com/public/practiceguidelines/headache_gl.htm. Accessed October 2001.
30. Ramadan NM, Silberstein SD, Freitag FG, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. The U.S. Headache Consortium, American Academy of Neurology. April 2000. Available at: http://www.aan.com/public/practiceguidelines/headache_gl.htm. Accessed October 2001.
31. Matchar DB, Young WB, Rosenberg JH, et al. Evidence based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. The U.S. Headache Consortium, American Academy of Neurology. April 2000. Available at: http://www.aan.com/public/practiceguidelines/headache_gl.htm. Accessed October 2001.
32. Manek NJ, Lane NE. Osteoarthritis: current concepts in diagnosis and management. Am Fam Physician. March 15, 2000;61(6):1795-1804. Review.
33. Preboth M. Management of pain in sickle cell disease. Am Fam Physician. March 1, 2000;61(5):1544, 1549-1550.
34. Morey SS. Guidelines on migraine: part 2. General principles of drug therapy. Am Fam Physician. October 15, 2000;62(8):1915-1917.
35. Morey SS. Guidelines on migraine: part 3. Recommendations for individual drugs. Am Fam Physician. November 1, 2000;62(9):2145-2148, 2151
36. Morey SS. Guidelines on migraine: part 4. General principles of preventive therapy. Am Fam Physician. November 15, 2000;62(10):2359-2360, 2363.
37. Morey SS. Guidelines on migraine: part 5. Recommendations for specific prophylactic drugs. Am Fam Physician. December 1, 2000;62(11):2535-2539. Review.

38. Institute for Clinical Systems Improvement (ICSI) Work Group. Diagnosis and Treatment of Adult Degenerative Joint Disease (DJD) of the Knee. ICSI health care guideline. November 2000.
39. Institute for Clinical Systems Improvement (ICSI) Work Group. Migraine Headache. ICSI health care guideline. May 2000.
40. Pellegrini JE, Paice J, Faut-Callahan M. Meperidine utilization and compliance with Agency for Health Care Policy and Research guidelines in a tertiary care hospital. CRNA. 1999;10(4):174-180.
41. Carr DB, Miaskowski C, Dedrick SC, et al. Management of perioperative pain in hospitalized patients: a national survey. J Clin Anesth. 1998;10(1):77-85.
42. Data from multihospital study show low compliance with pain management protocols. Data Strateg Benchmarks. June 1999;3(6):91-93.
43. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med. 1994 3;330(9):592-596.
44. Cleeland CS, Gonin R, Baez L, et al. Pain and treatment of pain in minority patients with cancer. The Eastern Cooperative Oncology Group Minority Outpatient Pain Study. Ann Intern Med. 1997;127(9):813-816.
45. Stratis Health. Stratis Health-Medicare Health Care Quality Improvement Project: Cancer Pain Assessment and Management in the Hospital Setting. Bloomington, MN: Stratis Health; 1997.
46. Rischer JB, Childress SB. Cancer pain management: pilot implementation of the AHCPR guideline in Utah. Jt Comm J Qual Improv. 1996; 22(10):683-700.
47. Du Pen SL, Du Pen AR, Polissar N, et al. Implementing guidelines for cancer pain management: results of a randomized controlled clinical trial. J Clin Oncol. 1999;17(1):361-370.
48. Harwood KJ, Nordin M, Heibert R, et al. Low back pain assessment training of industry-based physicians. J Rehabil Res Dev. 1997;34(4):371-382.
49. Joint Commission on Accreditation of Healthcare Organizations. Pain management standards. Effective January 1, 2001. Available at: http://www.jcaho.org/standard/pain_hap.html. Accessed September 2001.
50. Gordon DB, Dahl JL, Stevenson KK . Introduction. In: Gordon DB, Dahl JL, Stevenson KK, eds. Building an Institutional Commitment to Pain Management. The Wisconsin Resource Manual. 2nd ed. Madison, WI: University of Wisconsin-Madison Board of Regents; 2000.
51. American Pain Society Quality of Care Committee. Quality improvement guidelines for the treatment of acute pain and cancer pain. JAMA. 1995; 23:1874-1880.

NATIONAL
PHARMACEUTICAL
COUNCIL, INC

1894 Preston White Drive
Reston, VA 20191
www.npcnow.org

Joint Commission
on Accreditation of Healthcare Organizations

One Renaissance Boulevard
Oakbrook Terrace, IL 60181
www.jcaho.org