

# CHRONIC PAIN MANAGEMENT: A DISEASE-BASED APPROACH



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## **Learning Objectives**

1. Perform a comprehensive assessment of a pain complaint and determine the most likely pathogenesis of the pain.
2. Describe pathophysiology, clinical presentation, diagnosis, and prognosis of common chronic pain conditions, including osteoarthritis (OA), peripheral diabetic neuropathy (PDN), post-herpetic neuralgia (PHN), low back pain (LBP), and spinal cord injury (SCI) pain.
3. Establish an appropriate therapeutic goal for a patient with chronic pain, including functional goals.
4. Develop a therapeutic plan with attention to economic, practical, and patient-specific factors for common chronic pain conditions.
5. Develop strategies for evaluating therapeutic and potentially adverse outcomes of pain-relieving pharmacotherapeutic regimens, and managing adverse effects of therapy.

## **Introduction**

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” This definition acknowledges that pain is not determined by tissue damage alone; in fact, the sensation of pain is not correlated well with the degree of tissue injury. Pain complaints vary in intensity (mild, moderate, or severe), quality (sharp, stabbing, burning, or dull), duration (transient, intermittent, or persistent), and location (superficial or deep, localized, diffuse, or radiating). The complexity of pain as a clinical

syndrome is one of the reasons that our society provides less than optimal pain management. In fact, pain encompasses a sensory-discriminatory component (description of the pain itself), a motivational-affective component (such as anxiety or depression), and a cognitive-evaluative component (thought process regarding the cause and meaning of the pain). Pain is a highly individualized, subjective experience and was described by Margo McCaffery, a noted nurse pain-management clinician, as “whatever the experiencing person says it is, existing whenever he says it does.”

Pain may be considered acute, chronic malignant, or chronic nonmalignant. Chronic nonmalignant (CNMP), or persistent pain, is defined as pain that lasts more than 3–6 months, although others have defined chronic pain as that which exceeds the expected healing process from an acute insult. Chronic pain may be associated with persistent pathologic processes, or recur at intervals of months or years. Chronic nonmalignant pain is associated with nonlife-limiting conditions and pain from nondiscernable pathology. Examples include diffuse joint pain, chronic low back pain (LBP), failed back syndrome, chronic spinal cord injury pain, headache, myofascial pain syndrome, fibromyalgia, neuropathic pain states (e.g., painful diabetic neuropathy (PDN), post-herpetic neuralgia (PHN), phantom limb pain, complex regional pain syndrome) and arthritides (e.g., osteoarthritis [OA], rheumatoid arthritis, juvenile chronic arthritis, and systemic lupus erythematosus). In contrast, chronic malignant pain is associated with progressive disease that is potentially life-limiting, including pain caused by cancer and other advanced diseases.

Regardless of how it is defined, chronic pain is highly prevalent in our society. According to a 1999 Gallup survey, 90% of Americans 18 years or older reported experiencing pain at least once a month, and 42% of adults reported experiencing pain every day. Chronic pain is the leading

International Association for the Study of Pain. Pain Terms. Available at <http://www.iasp-pain.org/terms-p.html#Pain>. Accessed September 15, 2004.

# Abbreviations in this Chapter

AED	Antiepileptic drug
CNMP	Chronic nonmalignant pain
CNS	Central nervous system
COX	Cyclooxygenase
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GI	Gastrointestinal
LBP	Low back pain
NMDA	<i>N</i> -methyl-D-aspartate
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PDN	Painful diabetic neuropathy
PG	Prostaglandin
PHN	Post-herpetic neuralgia
PPI	Proton pump inhibitor
QST	Quantitative sensory testing
SCI	Spinal cord injury
SMR	Skeletal muscle relaxant
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

cause of adult disability in the United States and is the most common reason patients see a primary care clinician. Data from a multinational study showed that 22% of patients reported persistent pain when presenting to their primary care physician, and that these patients were more likely to have an anxiety or depressive disorder, to experience significant activity limitations, and to have unfavorable health perceptions. Pain, like quality of life, is multidimensional. Unremitting pain can adversely affect all aspects of quality of life, including physical, psychological, social, and spiritual functioning. A comprehensive assessment of pain includes all four elements.

## Pathophysiology of Pain

Pain can be divided into two categories: adaptive and maladaptive. Acute pain from a noxious stimuli (such as an injury) is an example of adaptive pain, which contributes to survival by protecting the organism from injury or promoting healing. Maladaptive pain is an example of nervous system pathology, or pain as disease.

Although pain is frequently thought of as a single entity, it is now known that several distinct types exist: nociceptive, inflammatory, neuropathic, and functional. Greater knowledge of the mechanisms of pain will enhance the practitioner's ability to select the best analgesic agent.

### Nociceptive Pain

Nociception is the term used to describe how processing stimuli that damage normal tissue (or have the potential to do so if prolonged) becomes a conscious experience. Nociceptive pain has positive value; it is an alarm system that heralds the presence of a potentially damaging stimulus. Individuals with congenital insensitivity to pain lack this protective function and often experience self-induced mutilation of the lips and tongue, pressure ulcers, and loss of fingertips.

Nociception is defined as the transmission of noxious stimuli, known as nociceptive impulses, from the site of insult to the central nervous system (CNS). When this noxious stimuli reaches the level of consciousness, it is considered "pain." This represents the sensory component of pain, which is influenced by the emotional component of pain (e.g., anxiety or depression, other sensory input, and nociception itself). Nociception is described as having four components: transduction (changing noxious stimuli in sensory nerve endings to impulses), transmission (the movement of impulses from the site of transduction to the brain), perception (recognizing, defining and responding to pain), and modulation (activation of descending pathways that exert inhibitory effects on pain transmission) (see Figure 1-1).

### Transduction

Primary afferent neurons, known as nociceptors, are distributed throughout the periphery. When the nociceptors (known to laypeople as "nerve endings") are exposed to noxious stimuli, tissue damage may occur. The noxious stimuli, which may be mechanical, thermal, physical, or chemical, result in tissue injury. Tissue injury then leads to the release of chemical mediators, such as bradykinin, potassium ions, histamine, and serotonin, which in turn triggers the release of prostaglandins (PGs), norepinephrine, epinephrine and substance P. All of these chemical mediators work to activate and sensitize nociceptors, causing local tissue reactions such as edema, vasodilation, and inflammation.

An action potential is required for the pain stimulus to move from the periphery to the spinal cord. The tissue injury that initiates nociception causes changes that depolarize and sensitize the nerve endings; subsequently, less intense noxious stimulation is required to maintain depolarization than that which initiated the whole process. Transduction is complete once the impulse is ready for transmission to the spinal cord.

Knowledge of the chemical mediators of nociception (e.g., substance P, bradykinin, prostaglandins, and others) and ions involved with depolarization (such as the influx of sodium and efflux of potassium) enable the practitioner to see how and where analgesics act. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit PG activity. Antiepileptic drugs (AEDs) may act by blocking or modulating sodium channels and slowing the nociceptive process.

Gureye O, Korff V, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. JAMA 1998;280:147-51.

Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140:441-51.

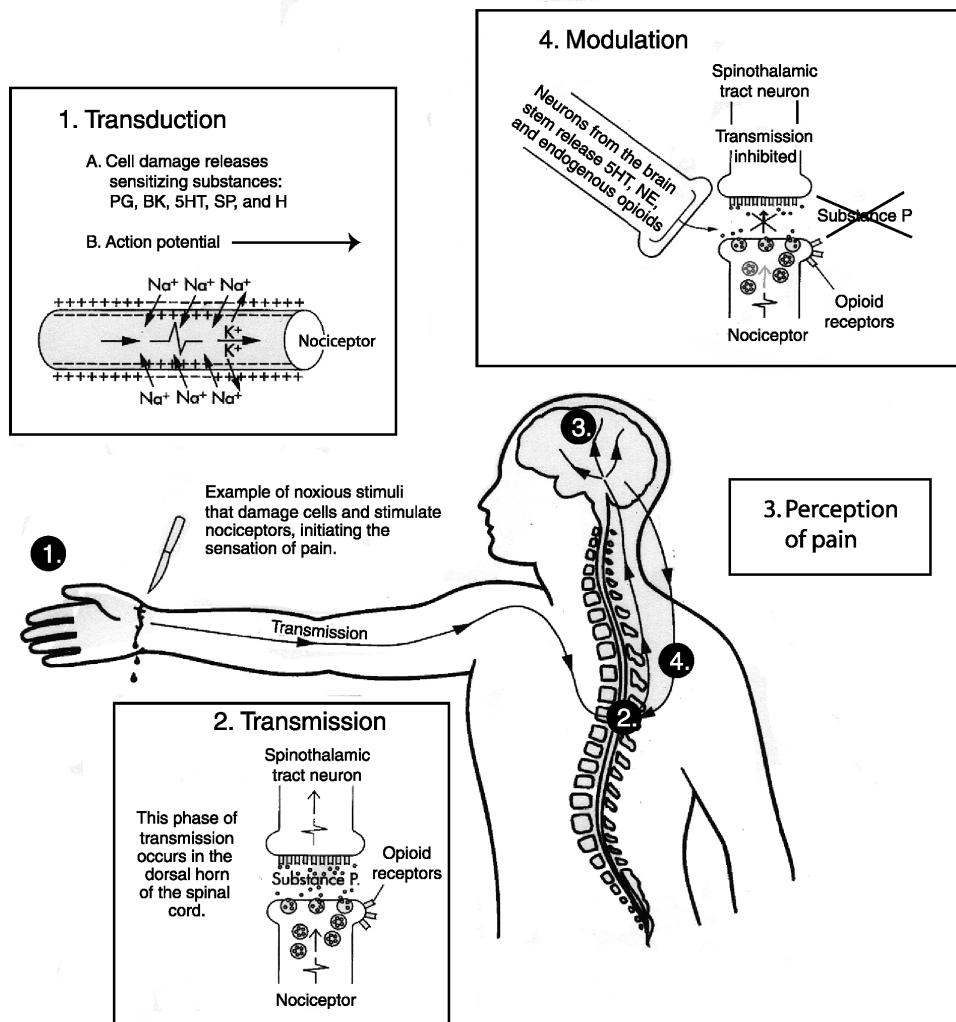


Figure 1-1. Nociception: basic process of normal pain transmission.

5HT = serotonin; BK = bradykinin; H = histamine; Na = sodium; NE = norepinephrine; PG = prostaglandin; SP = substance P.

Reprinted with permission from Elsevier. 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: Mosby, 1999:21.

Nociceptive pain originates from transduction at nociceptors. Pain that results from damage to the afferent nociceptive nerve fibers is neuropathic pain and does not begin at nociceptors.

### Transmission

When transduction is complete, the impulse travels to the spinal cord, then to the brainstem and thalamus, and eventually to the cortex. The afferent nociceptive fibers responsible for transmission from the periphery to the spinal cord are the A delta and C fibers. A delta fibers are fast-conducting, larger diameter, myelinated fibers that transmit sharp, well-localized pain. These afferent fibers are sensitive predominantly to mechanical and thermal stimuli. C fibers are slow-conducting, small in diameter and unmyelinated, transmitting dull, aching, poorly localized pain. Afferent C fibers are sensitive to mechanical, thermal, and chemical stimuli. These fibers terminate in the dorsal horn of the spinal cord, releasing neurotransmitters such as substance P,

glutamate, aspartate and others that bind to neurokinin-1 and *N*-methyl-D-aspartate (NMDA) receptors on the postsynaptic nerve membrane in the dorsal horn. Analgesics such as opioids may act at this point in the pain process to block the release of the neurotransmitters, particularly substance P. Drugs that are NMDA antagonists also work at this level by inhibiting the binding of excitatory amino acids, such as glutamate.

When the neurotransmitters bind to the postsynaptic receptor in the dorsal horn, the pain impulse is sent along ascending fiber tracts that terminate in the brainstem and thalamus. The thalamus then acts as a relay station, sending the pain impulse to higher cortical regions where it is processed.

### Perception

The third stage of nociception, perception, is the end of the neural activity of pain transmission. At this point, the impulse becomes a conscious experience or pain. It is not

entirely clear how or where in the brain pain is perceived, or why the response varies subjectively among subjects. Involved structures are likely the reticular system (responsible for autonomic response to pain), the somatosensory cortex (localizes and characterizes pain), and the limbic system (responsible for the emotional and behavioral response to pain).

Several factors can alter the perception of pain. The same pathways used to process nociceptive pain are used to process other input from the periphery, and the brain can process only a limited number of signals. Techniques such as distraction, relaxation, and imagery may be useful in treating pain because they competitively limit the number of pain signals attempting to reach the cortex for processing.

### Modulation

The last stage in nociception is modulation, changing or inhibiting pain impulses. Fibers that travel descending pathways from the brainstem to the dorsal horn of the spinal cord release substances such as endogenous opioids (e.g., enkephalins and endorphins), serotonin, norepinephrine, gamma-aminobutyric acid (GABA), and neurotensin. These substances affect analgesia by inhibiting the transmission of noxious stimuli.

When we hit our “funny bone,” the automatic response is to rub the painful area, which activates non-nociceptive neurons, which inhibit the transmission of nociceptive information. Application of heat or cold to a painful area is another example of how the transmission of nociceptive information is diminished.

Some analgesics affect the modulation stage of nociception. Exogenously administered opioids bind to opioid receptor sites and prevent the release of neurotransmitters, such as substance P. Adjunctive analgesics, such as antidepressant drugs, increase the availability of norepinephrine and serotonin, leading to inhibition of noxious stimuli. Baclofen, a GABA receptor substrate, is useful in treating painful spastic conditions.

### Inflammatory Pain

If the nociceptive defense system fails to protect against noxious, damaging stimuli and tissue damage occurs, the body shifts attention to healing the injured tissue. Inflammatory pain is an adaptive mechanism that facilitates achieving this goal by increasing sensitivity to stimuli to the affected area. Previously nonpainful stimuli are now perceived as painful. The adaptive response is to prevent contact with, or movement of, the injured area until healing is complete. With healing, inflammatory pain abates and resolves. Examples of inflammatory pain are trauma (including postoperative pain) and conditions with ongoing inflammation such as the arthritides, especially rheumatoid arthritis.

This heightened sensitivity to normally nonpainful stimuli is attributed to three factors: peripheral sensitization, phenotypic switch, and central sensitization.

### Peripheral Sensitization

With tissue injury or inflammation, multiple chemical mediators are released by damaged and inflammatory cells. This inflammatory soup is composed of adenosine

triphosphatase and potassium ions released intracellularly from damaged cells, as well as from cytokines, chemokines, and growth factors produced by inflammatory cells at the site of damage. Some of these chemical mediators activate the nociceptor terminal directly to produce pain, whereas others sensitize the nociceptive terminal, which becomes hypersensitive to subsequent stimuli. This hypersensitivity allows for much easier activation of the pain pathway, an adaptive mechanism until the tissue heals.

Cyclooxygenase-2 (COX-2), among other enzymes, is inducible and not constitutively present in most noninflamed tissues. The COX-2 is induced in response to interleukin-1 $\beta$  and tumor necrosis factor  $\alpha$ , and leads to the formation of prostaglandin E2 (PGE<sub>2</sub>), a sensitizing drug. For example, production of PGE<sub>2</sub> secondary to a sunburn results in a decreased threshold of pain induced by heat; therefore, a warm shower evokes burning pain in the affected area. Similarly, peripheral sensitization also accounts for a reduced threshold of pain due to heat in affected areas early in the course of PHN.

It is clear that NSAIDs or COX-2 selective drugs are beneficial in reducing inflammatory pain; however, their activity may be incomplete due to the presence of other peripheral sensitizers (e.g., nerve growth factor or bradykinin).

### Phenotypic Switch

In response to tissue damage and inflammation, a significant alteration occurs in the chemical composition and properties of the neurons that innervate inflamed tissues. These alterations reflect the nature and levels of the different proteins expressed by the sensory neurons. Altered production of these proteins may modify the phenotypes of the neurons, changing their transduction and transmission properties.

### Central Sensitization

Inflammatory pain is also associated with an increase in the excitability or responsiveness of neurons within the CNS, referred to as central sensitization. This phenomenon, like peripheral sensitization, is a major cause of hypersensitivity to pain after injury.

Central sensitization facilitates and increases the synaptic transfer from the nociceptive neurons, which occurs in two phases. The immediate phase of central sensitization is activity dependent; it is triggered by nociceptor input into the spinal cord. Within seconds of overwhelming sensory inflow from an injured tissue (such as a surgeon cutting through skin with a scalpel) or damaged nerve, receptive spinal cord neurons become hyperresponsive. Glutamate-activated NMDA receptors become phosphorylated during central sensitization, resulting in an increased number of NMDA receptors at the synaptic membrane, which have an enhanced responsiveness to glutamate. This increase in cell excitability results in normally innocuous stimuli, such as light skin touch, causing pain (e.g., allodynia; see Table 1-1). Hyperalgesia, an increased response to a painful stimulus, as well as secondary hyperalgesia (pain in areas well outside of the injured area), may occur. The NMDA receptor can significantly increase (up to 20-fold) the response of dorsal horn neurons, persisting even after

peripheral input stops. Known as wind-up pain, the NMDA receptor switches a low level of pain to a high level of pain perception, perpetuating the pain state.

The late phase of central sensitization is characterized by activation of transcription factors that enhance gene expression, resulting in long-lasting changes in dorsal horn neuronal function. Some changes in gene expression are driven by input from injured tissue such as the endogenous opioid peptide dynorphin.

Of importance, it is now recognized that prostanoid activity is significantly involved in central sensitization as seen with peripheral sensitization. The expression of COX-2 in CNS neurons occurs several hours after peripheral tissue injury. This expression is initiated by a circulating humoral factor released by inflammatory cells, which stimulates the production of interleukin-1 $\beta$ , and ultimately COX-2.

Prostaglandins, such as PGE<sub>2</sub>, act presynaptically and postsynaptically to increase excitability of central neurons. Specifically, PGE<sub>2</sub> increases presynaptic neurotransmitter release and produces direct depolarization of dorsal horn neurons postsynaptically. In addition, PGs reduce inhibitory transmission by acting on the glycine receptor.

Centrally active PGs produced by widespread COX-2 induction also cause fever and likely play a role in mood alteration, sleep disturbances, loss of appetite, and the generalized aches and pains that constitute the sickness syndrome, which is a feature of inflammatory disease.

## Neuropathic Pain

Neuropathic pain is an example of maladaptive pain, caused by damage to the nervous system. As described earlier, nociceptive pain results from direct stimulation of afferent nerves. Neuropathic pain originates from direct neuronal injury, resulting in disturbance of function or pathologic change in a nerve.

According to the International Association for the Study of Pain, the term neuropathic pain is used to describe painful syndromes that are “initiated or caused by a primary lesion or dysfunction in the nervous system.” Depending on where the nervous system lesion or dysfunction occurs, neuropathic pain is considered to be peripheral or central, although both components of the nervous system are likely involved. Examples of peripheral neuropathic pain syndromes include diabetic neuropathy, PHN, complex regional pain syndrome, chemotherapy-induced neuropathy, human immunodeficiency virus sensory neuropathy, phantom limb pain, postmastectomy pain, trigeminal neuralgia, and neuropathy secondary to tumor infiltration. Central neuropathic pain syndromes include examples such as central poststroke pain, pain associated with multiple sclerosis or Parkinson’s disease, and spinal cord injuries (SCIs).

Neuropathic pain may be stimulus-evoked or spontaneous stimulus-independent in nature. Spontaneous pain may be constant, intermittent, or paroxysmal, and most patients describe the pain as constant burning plus intermittent pain that is “shooting” or “electric shock-like.” The pain may be accompanied by spontaneous paresthesias and dysesthesias. Stimulus-evoked pain may be caused by light touch, pressure of clothing, wind, hot or cold

**Table 1-1. Selected Abnormal Sensory Signs and Symptoms With Neuropathic Pain States**

**Allodynia**—Pain due to a stimulus that does not normally provoke pain.

Comments: Best defined in terms of clinical response, allodynia is a change in the quality of a sensation (including tactile or thermal). The original response to a stimulus elsewhere in the body elicits pain referred to as allodynia in the affected area.

**Paresthesia**—An abnormal sensation, whether spontaneous or evoked.

Comments: Paresthesia describes the abnormal sensation that is not unpleasant, in contrast to dysesthesia (below), which is an unpleasant abnormal sensation.

**Dysesthesia**—An unpleasant abnormal sensation, whether spontaneous or evoked.

Comments: Dysesthesia is always an unpleasant abnormal sensation (compared with paresthesia which is just an abnormal, although not unpleasant, sensation). Hyperalgesia and allodynia are examples of dysesthesia.

**Hyperalgesia**—An increased response to a stimulus that is normally painful.

Comments: Hyperalgesia describes a heightened painful response to a mildly or moderately noxious stimuli. In contrast, allodynia is pain in response to a normally nonpainful stimulus.

**Secondary Hyperalgesia**—The spread of sensitivity to noninjured areas.

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

Comments: May occur with hyperesthesia (increased sensitivity to stimulation, excluding special senses), hyperalgesia or dysesthesia. Pain is often explosive in character.

International Association for the Study of Pain; Available at <http://www.iasp-pain.org/dict.html#RTFToC3>. Accessed September 12, 2005. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004;140:441–51.

temperatures, or other seemingly benign events. On physical examination, patients may exhibit sensory loss, such as loss of pinprick, thermal, tactile, or vibratory sensation. Positive physical findings may include allodynia (pain from a nonnoxious stimulus), and hyperpathia (exaggerated pain from a noxious stimulus).

Multiple pain mechanisms are responsible for the clinical syndrome of neuropathic pain, including central sensitization and phenotypic switching (as discussed in inflammatory pain), as well as ectopic excitability, augmented facilitation of sensory transmission, structural reorganization of the nervous system, and disinhibition (pathologic loss of inhibition) to pain response.

Although not clearly understood, the controls exerted by the brain on sensory processing in the spinal cord are both inhibitory and facilitatory. Some data suggest that descending facilitatory influences are activated or augmented after both inflammation and peripheral nerve injury. Descending inhibitory mechanisms mediated by neurotransmitters such as glycine and GABA focus sensory input to produce a limited, appropriate response. Central sensitization not only increases hypersensitivity to pain, but also causes pathologic loss of pain inhibition (known as disinhibition), especially currents mediated by GABA.

## Ectopic Excitability

Within weeks to months of peripheral nerve injury, nerve regeneration occurs. The damaged nerve may grow multiple nerve sprouts, some of which may form neuromas. The nerve sprouts and neuromas may begin to fire spontaneously in the absence of any peripheral stimuli; this effect peaks in intensity several weeks after the injury. This ectopic stimuli, or ectopic activity, is likely due to changes in the expression of sodium and potassium channels. After some time, atypical connections may develop between nerve sprouts in the area of nerve damage, resulting in "cross-talk" between somatic or sympathetic efferent nerves and nociceptors. These pathophysiologic changes result in spontaneous lancinating pain with bursts of activity and a tenderness and pins-and-needles sensation.

## Structured Reorganization

Nociceptive sensory neurons (that transmit pain) terminate in the most superficial laminae of the dorsal horn. Low-threshold sensory fibers that are activated by touch, pressure, vibration, and normal temperature exposure terminate in the deep laminae of the dorsal horn. Research has shown that peripheral nerve injury results in structural reorganization of the circuitry of these neurons. Several weeks after peripheral nerve injury, new growth of the central terminals of the low-threshold afferents is seen in the area where nociceptive terminals usually terminate exclusively. This structured reorganization, along with central sensitization and loss of inhibition, explains findings associated with neuropathic pain such as allodynia and hyperpathia.

## Functional Pain

Functional pain is a term used to describe those painful syndromes where no neurologic deficit or peripheral pathology is detected. The pain is due to an abnormal responsiveness of the nervous system, and may include processes such as central sensitization, reduced inhibition, and enhanced facilitation of pain. Examples of functional pain include fibromyalgia, irritable bowel syndrome, tension-type headaches, and some forms of noncardiac chest pain.

# Analgesics

Analgesics are generally divided into nonopioid drugs (e.g., acetaminophen, NSAIDs, or COX-2 inhibitors), opioids, and adjuvant drugs (e.g., antidepressant drugs, AEDs, antiarrhythmic drugs, and others).

## Nonopiod Analgesics

### Acetaminophen

Acetaminophen, one of the most widely used analgesic drugs worldwide, is used as monotherapy and in combination with other nonopiods such as aspirin, caffeine, salicylamide, and others to treat mild acute and chronic pain. Moderately painful conditions can be effectively

treated with acetaminophen when combined with an opioid (e.g., oxycodone and acetaminophen, codeine and acetaminophen).

Acetaminophen has analgesic and antipyretic activity, but lacks antiplatelet and peripheral anti-inflammatory effects. This drug is reviewed in detail in the Rheumatology: Osteoarthritis and Rheumatoid Arthritis chapter. The mechanism of action of acetaminophen is not completely understood. It may act by inhibiting PGs by way of COX-2 and nitric oxide in the CNS. Another theory is that acetaminophen acts to inhibit COX-3, which is only expressed centrally.

A variety of acetaminophen doses and dosing intervals has been approved, ranging from 325 mg every 4 hours to 1 g every 6 hours. For chronic pain that is responsive to acetaminophen, patients may enjoy enhanced quality of life by taking two 650-mg extended-release gelcaps every 8 hours.

Regardless of the dosage formulation used, the total daily dose of acetaminophen should not exceed 4 g. Acetaminophen is generally well tolerated and rarely produces serious adverse effects. Acute overdose of acetaminophen may cause fatal hepatic necrosis. Chronic overdosing of acetaminophen in excess of 4 g/day, or therapeutic dosing in the presence of other risk factors, may result in acetaminophen toxicity. Risk factors include concurrent use of alcohol, use by patients with pre-existing liver disease, those taking hepatotoxic substances, and patients who are fasting. Toxicity is primarily hepatic, but renal toxicity has also been associated with acetaminophen use, including interstitial kidney damage. Patients and practitioners must be mindful of the ubiquitous nature of acetaminophen in prescription and nonprescription products. For example, acetaminophen given in combination with an opioid limits the utility of the opioid, due to the need to adhere to a maximum daily dose of 4 g acetaminophen.

Acetaminophen is relatively free of drug interactions, but doses greater than 2.275 g/week may increase the international normalized ratio in patients taking warfarin. The precise mechanism of this interaction is not clear, but is likely due to acetaminophen-induced inhibition of warfarin metabolism by inhibition of the cytochrome P450 enzyme system. The relevance of this drug interaction is unclear; acetaminophen is still preferred over NSAIDs in patients receiving warfarin.

### Nonsteroidal Anti-inflammatory Drugs

The NSAIDs comprise a diverse group of 20 or more compounds that are extensively prescribed to treat acute and chronically painful conditions. The NSAIDs have analgesic, antipyretic, and anti-inflammatory actions.

As discussed in the pathophysiology section, PGs have a significant presence in the inflammatory soup associated with nociception, as well as peripheral and central sensitization. The NSAIDs inhibit peripheral and central PG production and therefore are valuable analgesics in managing nociceptive, inflammatory, and functional pain.

Chandrasekharan N, Dai H, Roos K, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. Proc Natl Acad Sci 2002;99:13926–31.

The COX isoenzymes are not expressed in neuropathic pain states and, unsurprisingly, do not significantly contribute to pain control in these conditions.

The mechanism of action of NSAIDs is also reviewed extensively in the Rheumatology: Osteoarthritis and Rheumatoid Arthritis chapter. Older, nonselective NSAIDs act by inhibiting both the COX-1 and COX-2 enzymes, resulting in both the therapeutic and toxic effects associated with NSAID therapy. Celecoxib is a COX-2 selective NSAID. Clinical research has shown that COX-2 selective NSAIDs are equally, but not more, effective than nonselective NSAIDs.

Adverse effects associated with NSAID therapy are comprehensively reviewed in the above noted Rheumatology chapter. Gastrointestinal (GI) complications range from minor gastric complaints (e.g., nausea, stomach upset, abdominal pain, anorexia, flatulence, and diarrhea) to serious complications (e.g., GI perforation, obstruction, and bleeding). One strategy to minimize GI complications includes the concurrent use of a gastroprotective agent. Misoprostol and proton pump inhibitors (PPIs) are commonly used for this purpose, and have been shown to be more beneficial than standard dose histamine-2 receptor antagonist therapy or other GI drugs. Unfortunately, misoprostol is used infrequently due to its high rate of adverse effects (e.g., abdominal cramping, flatulence, and diarrhea). Switching to a COX-2 selective NSAID may be beneficial, although there is a dearth of long-term data evaluating this outcome.

Cardiovascular complications associated with COX-2 selective and nonselective NSAIDs have received considerable media attention in the past few years. Events and data culminating in withdrawal of two COX-2 selective NSAIDs from the market (rofecoxib and valdecoxib) and actions imposed by the Food and Drug Administration (FDA) are reviewed in detail in the Rheumatology chapter. Specifically, the FDA concluded in its April 2005 announcement that the increased risk of cardiovascular events was likely a class effect of NSAIDs, and that changes in prescribing information were warranted for all NSAIDs. A boxed warning highlighting the potential for increased risk of cardiovascular and GI bleeding is now required of all prescription nonselective NSAIDs and celecoxib. Stronger warnings about these potential adverse effects are also required on the labeling of nonprescription NSAIDs.

Additional adverse effects associated with NSAIDs have been well characterized. Both nonselective and COX-2 selective NSAIDs cause adverse renal outcomes, including reduced renal blood flow and glomerular filtrate rate, and increased serum creatinine and blood urea nitrogen. Congestive heart failure, chronic renal insufficiency, cirrhosis with ascites, systemic lupus erythematosus, diuretic therapy, atherosclerosis and intravascular volume depletion increase the risk of renal toxicity with NSAIDs.

Nonselective NSAIDs inhibit platelet aggregation and increase bleeding time. This effect dissipates about five half-lives after discontinuing the nonselective NSAID with the exception of aspirin, which irreversibly inhibits platelet aggregation for the life of the platelet. Although COX-2 selective NSAIDs do not inhibit platelet aggregation, their prothrombotic effects make their lack of platelet inhibition less desirable. Nonacetylated salicylates, such as salsalate

and choline magnesium trisalicylate, do not significantly affect platelet aggregation. Sodium salicylate does not affect platelets but may increase prothrombin time.

The NSAIDs can cause CNS dysfunction such as headache, reduced attention span, loss of short-term memory, and difficulty with calculations. These effects are likely due to central PG inhibition.

Additional considerations for using NSAIDs and COX-2 inhibitors are presented in the Rheumatology chapter.

### Tramadol

Tramadol is a centrally acting drug with a dual mechanism of action. It weakly inhibits the reuptake of norepinephrine and serotonin at the level of the dorsal horn, and a major metabolite of tramadol is a weak mu opioid agonist. Neither mechanism alone is sufficient to justify the effectiveness of tramadol as an analgesic; synergism between the two mechanisms results in relief of moderate pain. Tramadol likely provides a greater degree of analgesia than nonopioid drugs (such as acetaminophen or NSAIDs), but has limited effectiveness relative to opioid analgesics.

Tramadol has been used to treat a variety of painful conditions, including those of neuropathic origin. Tramadol has been shown to significantly relieve pain in PDN and painful polyneuropathy of various causes.

The most common adverse effects with tramadol therapy are dizziness, vertigo, somnolence, headache, nausea, and constipation. Tramadol carries a low risk of causing seizures; the risk is increased in patients receiving supratherapeutic doses of tramadol, patients with a history of seizures, or patients taking other drugs that lower the seizure threshold. Use of tramadol with other serotonergic drugs (e.g., selective serotonin reuptake inhibitors [SSRIs]) and monoamine oxidase inhibitors may precipitate serotonin syndrome.

To decrease the incidence of adverse effects and increase patient adherence to therapy, tramadol should be initiated at low dosages, such as 50 mg/day, and increased every 3–7 days by 50–100 mg/day in divided dosages. The maximum dosage is 100 mg 4 times/day (300 mg/day in divided dosages for patients over 75 years old), and an adequate trial is 4 weeks.

Tramadol can cause or worsen cognitive impairment in older adults, and dosage adjustment is necessary in hepatic and renal disease. Initiating therapy with the combination tablet containing 37.5 mg tramadol plus 325 mg acetaminophen may cause fewer adverse effects, such as nausea and CNS effects, and may be more readily tolerated by fragile populations such as older patients and those with multiple comorbidities. Physical dependence and abuse of tramadol are rare; tramadol is a federally nonscheduled product.

### Opioids

Opioids are the mainstay of treatment in moderate to severe pain. Opioids are useful in treating all types of pain, are highly effective in treating nociceptive pain, and have a significant effect on neuropathic pain. Although the term opiate refers to substances derived from opium, the term opioids refers to opium-like substances. The term narcotic has historically been used to define opium and its derivatives but, at present, it is more a legal term referring

to abusable substances, including opioids. Practitioners should not refer to opioids as narcotic drugs when referring to their analgesic properties, as this may heighten patient fears of punitive action and suspicion. Rather, morphine and its relatives should be referred to as opioids.

Opioids relieve pain by binding to receptors throughout the CNS and GI tract, and to a lesser extent in peripheral tissues. By binding to and activating receptors in the CNS, exogenously administered opioids relieve pain in a mechanism consistent with the action of endogenous opioid peptides (dynorphins, endorphins, and enkephalins). The three primary opioid receptors are mu, delta, and kappa. Additional receptors such as sigma and epsilon have been identified, but they do not result in analgesia when stimulated. There are subtypes of mu, delta, and sigma receptors, and opioids vary in binding affinity, accounting for the variability in physiologic response to opioid therapy. Methadone is a mu opioid agonist, but also acts as an antagonist at the NMDA receptor, making it a particularly useful opioid to treat neuropathic pain.

Opioids can be classified as pure agonists, partial agonists, or mixed agonist-antagonists. Opioid antagonists are obviously not used to treat pain, but are used to reverse unfavorable effects of opioids (such as respiratory depression).

Pure opioid agonists, such as morphine, bind to and activate mu and kappa receptors, producing an analgesic effect that increases with dose without a ceiling effect. One exception is codeine. Although it is a pure mu opioid agonist, its use is limited by the development of adverse effects (such as nausea and constipation) and should not exceed 65–100 mg per dose or 400 mg/day by mouth. Codeine or codeine-containing analgesics are generally not considered first-line options for patients requiring chronic opioid therapy.

Partial agonists, such as buprenorphine, occupy only part of the mu opioid receptor, providing less analgesia than pure opioid agonists. Mixed agonist-antagonist opioids, such as butorphanol, partially activate the kappa receptor as an agonist and partially block the mu receptor. Both partial agonist and mixed agonist-antagonist drugs have limited clinical use due to a dose-ceiling effect. These drugs also should not be used in conjunction with a pure opioid agonist, as this may result in diminished analgesic effect or opioid withdrawal due to drug displacement.

The most feared adverse effect of opioid therapy, respiratory depression, is seen predominantly with opioid use for acute pain. Tolerance to respiratory depression usually develops within 5–7 days after starting around-the-clock dosing. Although respiratory depression is seldom associated with chronic opioid therapy, caution must be exercised with dosage increases and in patients at increased risk, such as patients with a history of pulmonary disease.

Sedation is commonly experienced by patients when starting opioid therapy or with each dosage increase. Frequently patients with chronic pain experience sleep deprivation, and when finally treated appropriately, they catch up on their sleep. Patients also develop tolerance to sedation in most cases within 4–5 days. Initiation of opioid

**Table 1-2. Definitions Related to the Use of Opioids for the Treatment of Pain**

**Addiction**

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

**Physical Dependence**

Physical dependence is a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

**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.

Reprinted with permission from the American Society of Addiction Medicine. A Consensus Document from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine. Available at <http://www.asam.org/ppol/paindef.htm>. Accessed September 14, 2005.

therapy, an increase in opioid dosage, or erratic as-needed dosing may also cause cognitive and psychomotor impairment. Patients should be counseled about this adverse effect and to use good judgment regarding potentially dangerous activities until tolerance develops. Once patients are on a stable opioid dose for at least a week and have not demonstrated any opioid-induced impairment, they are able to drive and perform other activities safely.

Adverse effects on the GI tract can be significant with opioid therapy. Nausea and vomiting may occur with any opioid, particularly when therapy is initiated and with dosage increases. Tolerance generally develops within several days of therapy; however, if the patient finds this intolerable, an antiemetic drug can be used for 48 hours, then as needed.

Constipation is a significant GI adverse effect, to which tolerance will not develop. This effect is caused by activation of mu opioid receptors in the colon, impairing intestinal motility. Practitioners should anticipate constipation as an adverse effect of opioid therapy and recommend appropriate prophylactic therapy. Hydration should be encouraged, along with regular use of a stimulant laxative (e.g., senna or bisacodyl). A stool softener, such as docusate, may also be beneficial. Bulk-forming laxatives are contraindicated as they may cause intestinal colic.

Opioids may also cause pruritus, although this is not generally an allergic reaction. Any opioid may cause this effect, although morphine seems to be implicated most commonly, and fentanyl is less likely to be a causative drug. Although pruritus can be treated symptomatically (e.g., antihistamine drugs), it is preferable to switch to a different opioid.

Patients, caregivers, and practitioners are frequently concerned about the risk of addiction to opioids. As shown in Table 1-2 the state of addiction, sometimes referred to as

Foley KM. Opioids and chronic neuropathic pain. *N Engl J Med* 2003;348:1279–81.

Gagnon B, Almahrei A, Schreier G. Methadone in the treatment of neuropathic pain. *Pain Res Manag* 2003;8:149–54.

psychological dependence, is quite different from physical dependence. The incidence of addiction to opioids is low in patients who do not have a previous history of substance abuse or psychiatric disorders that may increase the incidence of drug misuse (e.g., bipolar disorder or personality disorder). Another important clinical syndrome is pseudoaddiction, which refers to patient's behaviors that seem to be drug seeking, such as clock watching or even illegally obtaining analgesics. This behavior is actually pain relief-seeking behavior and may be distinguished from true addiction as behaviors resolve when the patient is treated effectively.

There are no data showing differences for all the mu opioid agonists in analgesic activity or pharmacodynamic action. However, pharmacogenomic differences among patients influence an individual patient's responsiveness to opioids. For example, people who are poor metabolizers of cytochrome P450 2D6 (about 10% of Caucasians) do not express the enzyme necessary to form the pharmacologically active O-demethylated metabolites of certain opioids such as codeine, dihydrocodeine, oxycodone, and hydrocodone, resulting in a diminished or absent therapeutic response.

Some mu opioid agonists are more potent than others on a mg-per-mg basis, but will confer a similar pharmacological effect if dosed equivalently. Table 1-3 is a listing of opioid dosage equivalencies. Practitioners need to recognize that there is not complete cross-tolerance to the pharmacological effects of the new opioid. Therefore, it is customary to reduce the newly calculated dose by 25–50% if the opioid switch was due to the development of an adverse effect, or dosage formulation issues. If the patient is having uncontrolled pain at the time of the opioid conversion, a dosage decrease due to lack of cross-tolerance is negated by the need to increase opioid due to poorly controlled pain.

Dosage calculations when converting from morphine to methadone are not linear. There are two possible explanations for why methadone becomes relatively more powerful with increasing prior exposure to other opioids. First, the configuration and chemical characteristics of methadone may cause a different type of binding to opioid receptors compared with opioids such as morphine, leading to only partial cross-tolerance to methadone. Second, methadone is a potent NMDA receptor antagonist and may reverse previously developed opioid tolerance. Regardless of the mechanism, it is critical to consider the nonlinear nature of dosage conversion calculations involving methadone.

The more morphine or morphine equivalents a patient is receiving, the more "potent" methadone is (see Table 1-4). For example, if a patient was receiving 60 mg/day of oral morphine, a 3:1 (3 mg oral morphine = 1 mg oral methadone) conversion would be used, which would be 20 mg/day of oral methadone. However, if a patient were receiving 750 mg/day of oral morphine, a 12:1 (12 mg of oral morphine = 1 mg of oral methadone) conversion would be used, or 62.5 mg/day of oral methadone. Methadone is generally dosed every 8 hours to control pain; therefore, the appropriate regimen in this example would be 20 mg orally every 8 hours.

Transdermal fentanyl may be a reasonable option for

patients with stable pain who are unable to take opioids by mouth, allowing continuous drug delivery without having to resort to parenteral opioid administration. The manufacturer's guidelines for conversion to transdermal fentanyl from other opioids are conservative. For example, the manufacturer of Duragesic recommends that 45–134 mg/day of oral morphine is equivalent to a 25 mcg/hour fentanyl patch. Most practitioners, however, would begin with a transdermal patch strength (in mcg/hour) equivalent to about 50% of the total daily oral morphine dose. For example, switching from MS Contin 60 mg orally every 12 hours, which is 120 mg of oral morphine per day would be a 50 mcg/hour transdermal fentanyl patch (about 50% of the total daily morphine dose).

It is important to consider the metabolic fate of opioids in this drug therapy decision-making process. All opioids are metabolized by the liver; therefore, a "start low and go slow" approach is appropriate for patients with liver impairment. The practitioner should acknowledge those opioids with active metabolites that may contribute to toxicity, particularly in patients with reduced renal function. For example, meperidine is metabolized to normeperidine, which causes neurotoxicities such as muscle twitching and jerking, seizures, coma, and death. For this reason, meperidine is generally not recommended, particularly for chronic use. Morphine has active metabolites that may contribute to persistent nausea, hallucinations, and myoclonus. Norpropoxyphene, the active metabolite of propoxyphene, accumulates and causes toxicity, and it is not a particularly efficacious analgesic. Therefore, these drugs should be used with caution or not at all in older adults and patients with renal impairment.

Oral opioids are short-acting (dosed every 4 hours) with the exception of those that have been pharmaceutically altered to be longer acting (e.g., morphine and oxycodone) and methadone. When opioids are used to treat chronic pain, they should be dosed in a time-contingent fashion (i.e., on a scheduled basis). If an oral long-acting or transdermal opioid is used as the basal opioid, it is generally useful to prescribe an opioid in an immediate-acting formulation for breakthrough pain (e.g., immediate-release morphine, oxycodone, and hydromorphone). This rapid-acting formulation is generally dosed as 10–15% of the total daily dose of the long-acting opioid. Patients should be encouraged to maintain a pain diary. If the breakthrough drug is used 2–3 times/day for several days, the patient should be re-evaluated, and the long-acting opioid increased if appropriate.

Once the patient is at steady-state with around-the-clock opioid dosing, if pain is not relieved, the total daily dose should be increased. As a guideline, the regularly scheduled dose is increased 25–50% if the pain is 5 or less (out of 10) or increased 50–100% if the pain is 6 or higher (out of 10). The practitioner should consider using the breakthrough opioid when doing these dosage calculations.

## Adjutants

Adjuvant analgesics include those drugs that are indicated for treatment of a condition other than pain, but have analgesic properties in some painful conditions. Adjuvants can be administered in combination with nonopioids and/or opioid analgesics, or as monotherapy to

**Table 1-3. Opioid Analgesics Starting Oral Dose Commonly Used for Severe Pain**

Name	Starting Oral Dose					Precautions and Contraindications
	Equianalgesic Dose (mg)	Oral <sup>a</sup>	Parenteral <sup>b</sup>	Adults (mg)	Children (mg/kg)	
<b>a. Morphine-like agonists (mu agonists)</b>						
Morphine	30	10		15–30	0.30	Standard of comparison for opioid analgesics. Sustained-release preparations (MS Contin, OramorphSR) release drug over 8–12 hours. Other formulations (Kadian and Avinza) last 12–24 hours. Generic sustained-release morphine preparations are now available.
Hydromorphone (Dilaudid)	7.5	1.5		4–8	0.06	Slightly shorter duration than morphine.
Oxycodone	20	—		10–20	0.30	
Methadone	10	5		5–10	0.20	Good oral potency, long plasma half-life (24–36 hours).
Levorphanol (Levo-Dromoran)	4 acute 1 chronic	2 acute 1 chronic		2–4	0.04	Long plasma half-life (12–16 hours, but may be as long as 90–120 hours after 1 week of dosing)
Oxymorphone (Numorphan)	—	1		—	—	5-mg rectal suppository about 5-mg morphine parenterally.
Meperidine (Dermerol)	300	75		Not recommended		Slightly shorter acting than morphine accumulates with repetitive dosing, causing CNS excitation; avoid in children with impaired renal function or who are receiving monoamine oxidase inhibitors. <sup>c</sup>
<b>b. Mixed agonist-antagonists (kappa agonists)</b>						
Nalbuphine (Nubain)	—	10		—	—	Not available orally, not scheduled under Controlled Substances Act.
Butorphanol (Stadol)	—	2		—	—	Like nalbuphine. Also available in nasal spray.
Pentazocine (Talwin)	50	30		—	—	
<b>c. Partial agonist</b>						
Buprenorphine (Buprenex)	—	0.4		—	—	Lower abuse liability than morphine; does not produce psychomimetic effects. Sublingual tablets now available both plain and with naloxone for opioid-dependent patient management by specially certified physicians. These tablets are not approved as analgesics.
<sup>a</sup> Starting dose should be lower for older adults.						
<sup>b</sup> These are standard parenteral doses for acute pain in adults and also can be used to convert doses for IV infusions and repeated small IV boluses. For single IV boluses, use half the IM dose. IV doses for children >6 months = parenteral equianalgesic dose × weight (kg)/100.						
<sup>c</sup> Irritating to tissues with repeated IM injection.						

For infants younger than 6 months, refer to the American Pain Society Guidelines (page 31).

CNS = central nervous system.

Reprinted with permission from the American Pain Society. American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 5th ed. Glenview, IL: American Pain Society, 2003.

**Table 1-4. Morphine: Methadone Equivalency Dosing**

Total mg/day Oral Morphine Equivalents	Conversion Ratio of Oral Morphine to Oral Methadone (mg Morphine:mg Methadone)
< 100 mg	3:1
101–300	5:1
301–600	10:1
601–800	12:1
801–1000	15:1
≥ 1001	20:1

Comments: Because methadone has a long terminal elimination half-life (up to 190 hours), which does not match the observed duration of analgesia (6–12 hours), there is a risk for drug accumulation, sedation, and respiratory depression. The conversion ratio between methadone and other opioids varies markedly depending on current opioid exposure. A recommended conversion table is shown above. Some practitioners may prefer to implement methadone over a 3-day period (increasing by one-third of total daily dose per day) while tapering off current opioid (cutting by one-third total daily dose per day).

Adapted with permission from the Medical College of Wisconsin. Fast Facts and Concepts #75 Methadone for the treatment of pain. Gazelle G, Fine PG. End-of-Life Physician Education Resource Center. September 2002. Available at [www.eperc.mcw.edu](http://www.eperc.mcw.edu). Accessed November 20, 2004. Von Gunten, CF. Fast Facts and Concepts # 86 . Methadone: Starting dose information. End-of-Life Physician Education Resource Center. March 2003. Available at [www.eperc.mcw.edu](http://www.eperc.mcw.edu). Accessed November 20, 2004.

treat CNMP conditions, particularly those with a neuropathic component. Although many drugs may fall into this group, the most common are AEDs, antidepressant drugs, antiarrhythmic drugs, local anesthetics, topical agents such as capsaicin, and a variety of miscellaneous drugs (e.g., NMDA antagonists, clonidine, and muscle relaxants). Adjuvant analgesics act through a variety of mechanisms, ultimately reducing peripheral or central sensitization, or enhancing the descending inhibitory pathway from the brain (see Figure 1-2).

### Antiepileptic Drugs

Antiepileptic drugs have long been used to treat neuropathic pain states. Early studies suggested that AEDs are the preferred adjunctive drugs to treat neuropathic pain that has more of a lancinating or paroxysmal component (as opposed to a burning, pins-and-needles type complaint); subsequent research has not confirmed this finding.

These drugs are often categorized as either first generation (carbamazepine, clonazepam, phenytoin, primidone, and valproate) or second generation (felbamate, gabapentin, lamotrigine, tiagabine, topiramate, and others). Mechanisms of action vary among these drugs and frequently overlap. The spectrum of mechanisms involves voltage-gated ion channels (sodium channels and calcium channels), ligand-gated ion channels, combined voltage/ligand-gated channels, glutamate, NMDA receptors, GABA, and glycine. Specifically, these drugs block sodium and calcium currents, enhance GABA, and block NMDA receptors.

Beydoun A, Backonja M. Mechanistic stratification of antineuronal agents. J Pain Symptom Manage 2003;25(5S):S18–S30.

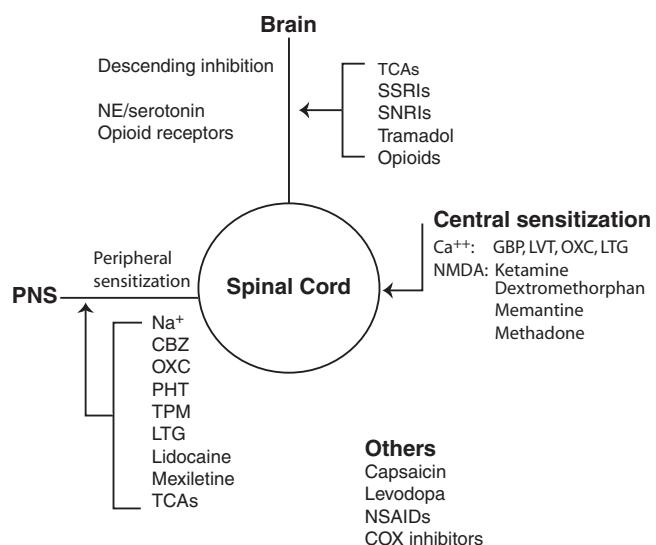


Figure 1-2. Mechanistic stratification of antineuronal agents.

Ca = calcium; CBZ = carbamazepine; COX = cyclooxygenase; GBP = gabapentin; LTG = lamotrigine; LVT = levetiracetam; Na = sodium; NE = norepinephrine; NMDA = *N*-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug; OXC = oxcarbazepine; PHT = phenytoin; PNS = peripheral nervous system; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TPM = topiramate.

Reprinted with permission from Elsevier. Beydoun A, Backonja M. Mechanistic stratification of antineuronal agents. J Pain Symptom Manage 2003;25(5S):S18–S30. © 2003 US Cancer Pain Relief Committee.

### First-generation AEDs

Carbamazepine was the first adjuvant drug to carry an indication for a painful condition—trigeminal neuralgia. Clinical research demonstrated the effectiveness for this indication, as well as diabetic neuropathy. The pain-relieving mechanism of carbamazepine is thought to be sodium channel blockade at the site of ectopic discharge in damaged or dysfunctional nerves. Unfortunately, the majority of patients complain of unacceptable adverse effects with carbamazepine, such as sedation and cognitive side effects, along with incomplete pain relief; therefore, it is not usually a first-line adjuvant therapy choice.

Phenytoin is thought to act in the same manner as carbamazepine and also has demonstrated effectiveness with trigeminal neuralgia and diabetic neuropathy. As with carbamazepine, patients report intolerable adverse effects and incomplete pain relief. Both phenytoin and carbamazepine require therapeutic drug monitoring. In addition, they are both potent inducers of the cytochrome P450 enzymes and implicated in many significant drug interactions. First-generation AEDs are seldom considered as first-line adjunctive drugs in the treatment of neuropathic pain.

### Second-generation AEDs

Due to the high degree of adverse effects and limited effectiveness with first-generation AEDs, their use has fallen off for the treatment of CNMP in favor of second-generation AEDs. These drugs have fewer adverse effects

and equivalent or better efficacy. The introduction of gabapentin led the way to expanding the role of AEDs in managing pain.

**Gabapentin.** Gabapentin is indicated for the treatment of PHN and has documented efficacy in treating PDN, cancer-related neuropathy, mixed neuropathic pain syndromes, phantom limb pain, Guillain-Barre syndrome, and acute and chronic pain from spinal cord injury. It is considered a first-line pharmacological intervention for neuropathic pain based on its proven efficacy and high degree of tolerability.

Research continues on the precise mechanism of action for gabapentin, but it is clear that its analgesic properties are not mediated by binding to GABA, opioid, dopamine, serotonin or neurokinin-1 receptors. Gabapentin also does not affect voltage-dependent sodium channels, nor does it reduce peripheral nerve discharges in animal models of neuropathic pain. It has increased the CNS concentration of GABA and can enhance the release of nonvesicular GABA. Regardless of the specific mechanism, gabapentin likely works within the CNS, probably at the level of the spinal cord. Gabapentin binds to a subunit of a voltage-dependent N-type calcium channel and to subunits in laminae I and II, the termination site of afferent nociceptors.

The most common adverse effects associated with gabapentin therapy include somnolence, dizziness, and generalized fatigue. Gabapentin may cause or exacerbate cognitive impairment in older adults, and gait and balance problems. Less commonly, patients complain of GI symptoms and peripheral edema.

To minimize adverse effects and enhance adherence to therapy, gabapentin should be initiated at low doses, such as 100 mg (for older adults) to 300 mg (for younger adults) in a single dose at bedtime or 100–300 mg 3 times/day, and titrated every 1–7 days by 100–300 mg as tolerated. Most patients will require 900–1800 mg/day, although occasionally patients may respond to lower doses (e.g., 300 mg once daily) and many patients require as much as 3600 mg/day. If the patient has had at least a partial response on 1800 mg/day, the upward titration should be continued to as high as 3600 mg/day (1200 mg 3 times/day) as tolerated. It may take 3–8 weeks for appropriate titration, and 1–2 weeks should be allowed at maximum dose to assess therapeutic response. Titration and maximum daily dosage should be adjusted in patients with renal impairment (see Table 1-5).

**Other Second-generation AEDs.** Other new AEDs have also been used in managing neuropathic pain, including

oxcarbazepine, gabitril, lamotrigine, topiramate, levetiracetam and zonisamide. Of these, lamotrigine has the best evidence of efficacy in the treatment of human immunodeficiency virus sensory neuropathy, trigeminal neuralgia, PDN, and central poststroke pain, and in a subgroup of patients with pain associated with incomplete spinal cord lesions. Despite this, lamotrigine is generally not considered as a first-line drug for neuropathic pain because of the slow and careful titration required and the risk of both severe rash and Stevens-Johnson syndrome associated with its use.

Data regarding the use of the other second-generation AED is largely anecdotal and uncontrolled. Early results are encouraging, however, and they remain second-line options for patients who do not respond to more proven AED therapy, such as gabapentin.

### Antidepressant Drugs

Antidepressant drugs, specifically the tricyclic antidepressants (TCAs), have long been used to treat neuropathic pain. These drugs act to modulate the descending inhibitory pathway from the brain and may have a variety of secondary effects. In addition, SSRIs, serotonin-norepinephrine re-uptake inhibitors (SNRIs), and other antidepressant drugs are effective in treating CNMP. Although the analgesic effects are independent of antidepressant effects, these drugs should be strongly considered in patients with both pathologies.

### Tricyclic Antidepressant Drugs

Before the introduction and widespread use of gabapentin and other drugs for neuropathic pain, TCAs were considered to be the gold standard for the treatment of neuropathic pain and are still considered to be first-line drugs. The TCAs are efficacious in treating pain independent of their ability to treat depression; the analgesic dose is generally 30–50% of the antidepressant dose. The TCAs can be divided into two categories: tertiary (amitriptyline, imipramine, doxepin, clomipramine, and trimipramine) and secondary (desipramine, nortriptyline, amoxapine, and protriptyline) amines.

The TCAs inhibit the re-uptake of the biogenic amines, norepinephrine and serotonin. The tertiary amines inhibit the reuptake of both norepinephrine and serotonin, whereas the secondary amines are relatively selective norepinephrine re-uptake inhibitors. Blocking norepinephrine reuptake in the CNS enhances endogenous pain modulation through

**Table 1-5. Gabapentin Dosing**

Renal Function CrCl (ml/min)	Total Daily Dose Range (mg/day)	Dose Regimen (mg)				
≥ 60	900–3600	300 TID	400 TID	600 TID	800 TID	1200 TID
> 30–59	400–1400	200 BID	300 BID	400 BID	500 BID	700 BID
> 15–29	200–700	200 QD	300 QD	400 QD	500 QD	700 QD
15 <sup>a</sup>	100–300	100 QD	125 QD	150 QD	200 QD	300 QD

<sup>a</sup>For patients with creatinine clearance < 15 ml/minute, reduce daily dose in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/minute should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/minute receive).

BID = 2 times/day; CrCl = creatinine clearance; QD = every day; TID = 3 times/day.

Reprinted with permission from Pfizer, Inc. Neurontin Package Insert. Available at [http://www.pfizer.com/download/uspi\\_neurontin.pdf](http://www.pfizer.com/download/uspi_neurontin.pdf). Accessed November 20, 2004.

descending spinal pathways; this effect is augmented by blocking serotonin reuptake. Blocking serotonin reuptake alone does not appear to be sufficient for analgesic purposes. Additional potential mechanisms include blocking and modulating sodium channels, and  $\alpha_2$ -adrenoreceptor agonist effects. It is likely that the TCAs act through both peripheral and central mechanisms.

The TCAs have been used to treat LBP, fibromyalgia, PDN, PHN, central pain, cancer pain, and headaches, including migraine. It is often heard that TCAs are preferred adjunctive drugs over AEDs for constant neuropathic pain (e.g. such as throbbing and burning complaints) versus lancinating pain; research has shown the TCAs to be effective in treating neuropathic pain across the spectrum. The secondary amines are as effective as the tertiary amines and have fewer adverse effects.

Primary side effects of the TCAs include significant anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention, cognitive impairment [memory, concentration], sedation, and orthostatic hypotension). They may also cause cardiac arrhythmias and must be used cautiously in patients with a history of cardiovascular disease, in addition to patients with histories of narrow angle glaucoma, urinary retention, and autonomic neuropathy. The secondary amines are less likely to cause anticholinergic and sedative effects than the tertiary amines. It is not advisable to use TCAs in patients with a history of suicide attempts or suicidal ideation. The TCAs are implicated in several drug interactions, including blocking the effects of some antihypertensive drugs (e.g., clonidine or guanethidine) and thereby diminishing the hypotensive effect. Most TCAs are metabolized by multiple P450 enzymes and are likely to be object drugs for drug interactions with many common drugs.

Although amitriptyline has been the most studied TCA, nortriptyline or desipramine are preferred choices due to fewer adverse effects. Nortriptyline specifically is equal in effectiveness to amitriptyline in the treatment of PHN, with better tolerability. Regardless of the TCA selected, patients over age 40 should receive a screening electrocardiogram to detect cardiac conduction abnormalities before beginning therapy.

Therapy should be initiated at a low dose: 10 mg at bedtime in a frail or older adult and 25 mg at bedtime in a younger patient. To optimize tolerability and adherence, the dose should be titrated slowly, adding an additional 10–25 mg to the single daily bedtime dose every 3–7 days. The customary effective dose is 75–100 mg at bedtime; practitioners may fail to recognize that a poor response or recurrence of pain is due to inadequate titration of the TCA. It may take several weeks for titration to the appropriate dose. Pain relief generally begins within 7–10 days; an adequate trial is at least 1–2 weeks at the maximum tolerated dose.

#### Selective Serotonin Reuptake Inhibitors

The SSRIs have fewer adverse effects and are better tolerated than the TCAs, but as a class they are not as effective in treating pain. Clinical trials have shown paroxetine and citalopram to be superior to placebo in PDN,

but not as effective as TCA therapy. Fluoxetine is not any more effective than placebo as an analgesic.

#### Serotonin-Norepinephrine Reuptake Inhibitors and Other Antidepressant Drugs

The SNRIs that have been systematically investigated for the treatment of neuropathic pain include venlafaxine and duloxetine. These drugs also inhibit the reuptake of biogenic amines; in this case, primarily norepinephrine.

Duloxetine has received FDA-labeled approval for treating PDN in addition to depression. This is the first adjunctive analgesic to carry this indication. Pivotal trials resulting in this approval showed superior pain relief compared with placebo, and the drug was relatively well tolerated. Primary adverse effects included nausea, constipation, dry mouth, and fatigue.

Venlafaxine has also been shown in clinical trials to be effective in treating PDN and painful polyneuropathy. Research evaluating venlafaxine versus placebo for managing chronic neuropathic pain after breast cancer surgery failed to show a difference in daily pain ratings, but did achieve statistical significance in several secondary pain end points.

Sustained-release bupropion has shown significant pain relief compared with placebo in treating various peripheral and central neuropathic pain syndromes.

Based on available data for SSRIs, SNRIs, and other antidepressant drugs, they can be considered when TCA therapy fails or is inappropriate, particularly for patients with a history of depression.

#### Antiarrhythmic Drugs and Local Anesthetics

Antiarrhythmic drugs and local anesthetics reduce neuropathic pain by sodium channel blockade. Local anesthetics include eutectic mixture of lidocaine and prilocaine cream and a 5% transdermal lidocaine patch (LidoDerm). This cream is generally used to prevent pain associated with venipuncture, and there are anecdotal reports of its use to treat localized neuropathic pain in patients with cancer.

Transdermal lidocaine has an approved labeling indication by the FDA for treating PHN; however, limited data have also shown it to be useful in treating myofascial pain syndromes, osteoarthritic knee pain, and PDN. As approved for PHN, the lidocaine patch is placed directly on painful areas for 12 hours on, followed by 12 hours off. Up to three patches are approved for simultaneous use, and they may be cut and shaped for application to affected areas. When applied to intact skin, as indicated, topical lidocaine does not accumulate in patients with normal hepatic function. Application of the lidocaine patch to burned, broken, or inflamed skin may result in enhanced absorption, leading to increased blood levels of lidocaine. Patients with severe hepatic dysfunction may have reduced capacity for metabolizing lidocaine, causing higher blood levels that may potentially be toxic. This formulation is generally well tolerated, with mild skin reactions, such as erythema or rash, being the primary adverse effect. Concurrent use of a class I antiarrhythmic drug (e.g., mexiletine) may increase the risk for toxicity.

In general, pain relief begins with application, but it may take several days to achieve a full effect. If the therapeutic goal is not achieved within 2 weeks, additional pain relief is unlikely.

Mexitilene is an oral lidocaine congener antiarrhythmic drug that has been evaluated for treating PDN with mixed results. Adverse effects include dizziness, palpitations, tremor, chest pain, arrhythmias, and GI disturbances. Mexilitene is not commonly used to treat CNMP.

### Topical and Other Adjuvant Analgesics

#### *Capsaicin*

Capsaicin, an enzyme found in hot chili peppers, has analgesic properties. The mechanism is depletion of substance P from sensory C fibers, and action as a counterirritant. Available in 0.025% and 0.075% strengths, capsaicin has been used to treat minor muscle and joint aches and pains associated with simple backache, arthritis, sprains, strains, and bruises. It has also shown benefits in treating OA pain and mixed results in treating rheumatoid arthritis pain. Mixed results have also been shown in using capsaicin to treat dorsal horn neuron and PDN.

Clinical trials with capsaicin cannot be blinded due to the primary adverse effect—burning on application. Patients must apply the product 4 times/day and must be educated that the burning will lessen as therapy continues. Another crucial counseling point is to wash hands thoroughly after application; touching mucous membranes or the eyes with an unwashed hand after capsaicin application may cause tissue damage and significant pain. Topical capsaicin is not routinely recommended for most patients, but some may achieve some pain relief.

#### *Other Adjunctive Analgesics*

As described in the pathophysiology section, the NMDA receptor plays a significant role in pain pathogenesis. With central sensitization, the glutamate-activated NMDA receptor is phosphorylated, increasing its distribution and responsiveness to glutamate. As a result, previously nonpainful stimuli (e.g., touch) result in pain (allodynia) and/or an exaggerated or amplified response (hyperalgesia). There is considerable enthusiasm for investigating the use of NMDA receptor antagonists, such as ketamine and dextromethorphan. Unfortunately, the widespread distribution of NMDA receptors in the brain results in unacceptable adverse effects with the use of these drugs. Ketamine has been associated with adverse psychotomimetic effects, and dextromethorphan (in much higher doses than that required for antitussive effects) causes nausea, mood alterations, and other adverse effects. Work continues in developing clinically useful NMDA receptor antagonists. As described earlier, methadone is an opioid with some NMDA receptor antagonism, making it an attractive option for managing mixed pain with a neuropathic component.

Skeletal muscle relaxants (SMRs) are effective adjunctive analgesics used to treat pain accompanied by muscle spasm. In general, SMRs are best used for up to a week; therapy that exceeds 2 weeks results in diminished effectiveness and increased CNS depression. Baclofen, a chemical analog of GABA, and tizanidine, an  $\alpha_2$ -agonist

sympathomimetic muscle relaxant, have been successfully used for longer time periods than older SMRs (e.g., carisoprodol). Adverse effects of SMRs include drowsiness, dizziness, light-headedness, fatigue, and sedation. Drugs such as carisoprodol and meprobamate have been associated with misuse and abuse.

Remaining adjunctive analgesics include autonomic drugs such as clonidine, botulinum toxins (to treat myoclonus, tension-type headache, myofascial pain, back pain, and other focal dystonias and spastic disease states), and corticosteroids (used to treat a variety of somatic, visceral, and neuropathic pain conditions and headache due to increased intracranial pressure).

Patients with chronic pain frequently turn to complementary and alternative interventions. Examples include aromatherapy, energy balancing therapies (such as acupressure, healing touch, reiki, and therapeutic touch), relaxation, imagery, and music therapy. Practitioners should also ask patients about their use of dietary supplements to treat pain. Modest evidence supports the use of glucosamine and chondroitin in managing OA. A variety of other dietary supplements have been used with varying degrees of success such as S-adenosylmethionine, devil's claw, ginger,  $\gamma$ -linoleic acid, and others.

## Assessment of Pain

Let us review the case of V.H. and the elements of assessing a complaint of pain:

V.H. is a 66-year-old African-American woman who asks for your advice about the selection of a heating pad she can use to reduce her pain. When you inquire about the pain, she tells you: "Well, it hurts just about all over. My knees hurt on and off all day long, and my feet hurt all the time, especially at night when they get really cold. I was hoping a heating pad would warm my feet at night, and take away some of the numb-like feeling. And I could use it during the day on my knees."

V.H. is tired-looking and obese. On further questioning, she tells you that she has had type 2 diabetes mellitus for about 15 years and arthritis for about 7 years. When you ask what her primary care physician's advice was, she responds, "He said if I lost weight, the pain in my knees would get better, and he said the foot pain was due to my sugar and nothing could be done about that."

### Pain Screening and Assessment

Because pain is such a prevalent complaint with significant consequences, health care providers should screen for pain at regular intervals. This includes every shift for inpatients and at every outpatient or home care visit for ambulatory individuals. Because there are many fears and myths about pain and its management, it is prudent not to limit questioning to the presence of pain but also to query about soreness, discomfort, and pressure, and to be as thorough as possible.

When the screening process discloses a potential pain complaint or a patient comes to a provider with a pain

complaint, an assessment is warranted. This includes any relevant diagnostic work-ups, a history and physical examination, assessment of the pain complaint itself, identification of the patient's goals and expectations for relief, and psychosocial assessment including barriers to pain relief or potentially aberrant behavior.

Despite V.H.'s complaint that "it hurts just about all over," she is actually describing two distinct pains. The first is the pain in her knees, likely related to her self-reported history of arthritis. The second pain is her complaint of the numb, cold, painful sensation in her feet, which her primary care provider said is due to diabetes. Let us review an assessment of V.H.'s pains.

### Knee Pain

You ask V.H. a series of questions to characterize her knee pain. Responses are as follows:

When asked to show you where the knee pain is, V.H. grasps both knee caps and rubs them. "The pain is right here in both knees." V.H. denies the pain moving to any other areas.

When you ask what brings on the knee pain, V.H. responds: "They are very stiff in the morning when I wake up, and it is hard to get around for 20 or 30 minutes. Then they limber up a little bit, but it hurts all the time. When the pain really gets bad, I sit down and rest, which helps. But when I sit for a while, like watching one of my programs on the television for about 30 minutes, my knees are very stiff again when I get up, and it takes about 10 or 15 minutes to work that out. Also, I do not need to watch the weather channel; my knees tell me when we are in for rainy weather."

In response to asking about what relieves the pain (nondrug interventions), V.H. tells you "just resting."

When asked to describe how the pain feels in her own words, she tells you it is "deep and aching."

V.H. is agreeable to using a Numeric Rating Scale (0 = no pain; 10 = worst imaginable pain) to rate the pain severity in her knees. She says at the worst it is a 7 out of 10, at the best it is a 3 out of 10. On average, the pain is a 4 or 5 out of 10.

Regarding the temporal aspects of her pain, V.H. tells you she has had knee pain off and on for about 7 or 8 years. She was diagnosed with OA about 7 years ago. The pain has been fairly constant for the past 6–8 months and varies in severity throughout the day.

You ask V.H. about any associated symptoms that accompany the knee pain. She tells you that it is disturbing that she can hear her knees creaking frequently. She says the pain does not make her nauseated or affect her appetite. Her sleep is interrupted due to pain, but mostly due to the foot pain (see below). She is anxious about her total pain picture (knees and feet). The knee pain specifically has adversely affected her functional ability. She is no longer able to spend the hour it takes to do grocery shopping because it hurts too badly to stand that long. She is unable to tend to her garden, as she cannot kneel down. Going upstairs is a burden, and she limits her trips to the second floor of her house to one trip at night. V.H. is considering moving her bedroom to the

first floor so she will not have to go upstairs. She also finds getting out of her car to be painful.

V.H. takes an occasional acetaminophen tablet, but it does not help. On average, she takes about 3–4 tablets/week (325 mg).

On physical inspection, V.H.'s knees are tender on palpation, although no swelling or warmth is noted. She has decreased range of motion and crepitus. Her quadriceps strength is diminished, particularly relative to her size. Laboratory values (erythrocyte sedimentation rate, hematocrit, and white blood cell count) are normal. Her primary care physician obtained x-rays of both knees, which showed loss of cartilage and osteophyte formation.

You explore V.H.'s health beliefs, cultural values (e.g., the meaning of pain and treatment goals), and any myths or misconceptions about pain management. She has no history of abusing alcohol, drugs, or other substances. She has no history of psychiatric disorders, or family history of alcoholism or drug addiction.

You ask V.H. what she would like to do that she cannot do now because of the knee pain. She tells you that she would like to remain independent in her own home. She also would like to grocery shop for herself and not rely on family and friends, and be able to go upstairs more easily. She realizes that she might not ever be able to kneel to garden in the yard again, but she would like to be able to move about her patio and pot flowers without pain. Functional impairment should always be queried, particularly when severity rating is 5 or higher on a 0–10 scale, as this has been shown to significantly affect functional status adversely.

### Foot Pain

You then turn to assessing V.H.'s complaint of numb, cold, painful feet that her primary care provider felt was related to her diabetes mellitus. Obviously, at this point you suspect PDN. Because neuropathic pain can encompass so many different qualities of pain, an assessment instrument that captures this information should be used. Some pain assessment instruments, such as the Short Form McGill Pain Questionnaire, contain items that capture multiple descriptions associated with neuropathic pain, but not the degree to which they are felt.

Several instruments have been developed to specifically evaluate neuropathic pain. The Neuropathic Pain Scale is most frequently cited. This validated instrument, shown in Figure 1-3, assesses distinct pain qualities associated with neuropathic pain and is sensitive to pharmacotherapeutic interventions used to treat neuropathic pain.

Back to the case of V.H., she describes her foot pain as burning in sensation most of the day, with a pins-and-needles, "creepy-crawly" type of sensation. This pain is located on the top of both feet and extends up her calves in both legs. At night her feet do not burn so much as turn cold. Nothing alleviates the pain, but she complains that contact with the bedsheets can precipitate the pain. As mentioned above, she occasionally takes acetaminophen, without relief. She has been experiencing this pain for the past year

**Instructions:**

There are several different aspects of pain which we are interested in measuring: pain sharpness, heat/cold, dullness, intensity, overall unpleasantness, and surface vs. deep pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how sweet a piece of pie might be (the intensity of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the intensity of a sensation is not the same as how it makes you feel. A sound can be quiet and “dull” or loud and “dull.”

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, how much it hurts and how unpleasant or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.

1. Please use the scale below to tell us how intense your pain is. Place an “X” through the number that best describes the intensity of your pain.

No pain	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most intense pain sensation imaginable

2. Please use the scale below to tell us how sharp your pain feels. Words used to describe “sharp” feelings include “like a knife,” “like a spike,” “jabbing,” or “like jolts.”

Not sharp	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most sharp sensation imaginable (like a knife)

3. Please use the scale below to tell us how hot your pain feels. Words used to describe very hot pain include “burning” and “on fire.”

Not hot	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most hot sensation imaginable (like fire)

4. Please use the scale below to tell us how dull your pain feels. Words used to describe very dull pain include “like a dull toothache,” “dull pain,” “aching,” and “like a bruise.”

Not dull	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most dull sensation imaginable

5. Please use the scale below to tell us how cold your pain feels. Words used to describe very cold pain include “like ice” and “freezing.”

Not cold	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most cold sensation imaginable (freezing)

6. Please use the scale below to tell us how sensitive your skin is to light touch or clothing. Words used to describe sensitive skin include “like sunburned skin” and “raw skin.”

Not sensitive	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most sensitive sensation imaginable (raw skin)

7. Please use the scale below to tell us how itchy your pain feels. Words used to describe very itchy pain include “like poison oak” and “like a mosquito bite.”

Not itchy	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most itchy sensation imaginable (like poison oak)

8. Which of the following best describes the time quality of your pain? Please check only one answer.

I feel a background pain all of the time and occasional flare-ups (break-through pain) some of the time.

Describe the background pain \_\_\_\_\_

Describe the flare-ups (break-through pain) \_\_\_\_\_

I feel a single type of pain all the time.

Describe this pain \_\_\_\_\_

I feel a single type of pain only sometimes. Other times, I am pain free.

Describe this occasional pain \_\_\_\_\_

9. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how unpleasant your pain is to you. Words used to describe very unpleasant pain include “miserable” and “intolerable.” Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how unpleasant your pain feels.

Not unpleasant	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most unpleasant sensation imaginable (Intolerable)

10. Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a “best guess,” but please give us your best estimate.

**How intense is your deep pain?**

No deep pain	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most intense deep pain sensation imaginable

**How intense is your surface pain?**

No surface pain	<input type="text"/> 0	<input type="text"/> 1	<input type="text"/> 2	<input type="text"/> 3	<input type="text"/> 4	<input type="text"/> 5	<input type="text"/> 6	<input type="text"/> 7	<input type="text"/> 8	<input type="text"/> 9	<input type="text"/> 10
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The most intense surface pain sensation imaginable

Figure 1-3. The neuropathic pain scale.

Reprinted with permission from the McGraw-Hill Companies. Galer BS, Dworkin RH. A Clinical Guide to Neuropathic Pain. Minneapolis: The McGraw-Hill Companies Inc., Healthcare Information Programs. 2000:42-44.

or so, increasing to current intensity. Using the Neuropathic Pain Scale, V.H. rates her foot pain as follows:

- Pain intensity—6 on average
- Sharpness of pain—5 on average
- Hotness of pain—an 8 during the day, 1 at night
- Dullness of pain—4 on average
- Coldness of pain—0 during the day, 6 during the night
- Sensitivity to light touch or clothing—ranges between 4 and 6, worse at night
- Itchiness of pain—an average of 1
- Overall unpleasantness of pain—6 on average
- Intensity of deep pain—2 on average
- Intensity of surface pain—8 on average

V.H. also complains that her shoes frequently feel too tight, and she feels as though she has ankle edema, although only minimal edema is noted on physical examination. V.H. does not offer any additional functional limitations due to the foot pain (over and above the knee pain), except stating she is anxious that this pain might indicate that she will likely require bilateral amputations at some point.

On physical examination, V.H. has decreased sensation to monofilament testing, diminished ankle and knee jerks, and reduced nerve conduction velocity (as determined from nerve conduction velocity testing). V.H. shows an exaggerated pain response to mildly painful stimuli. She exhibits decreased 2-point discrimination and decreased vibratory sensation. V.H. has diminished growth of hair on her toes, and reduced peripheral pulses in her lower extremities.

Continued in next column.

## **Pathogenesis of V.H.'s Pain**

Most OA pain is nociceptive; however, recent research has shown that OA is associated with local low-grade inflammation and few systemic effects. Clearly, PGs are significant mediators of pain and inflammatory stimuli at nociceptors. Osteoarthritis may also cause neuropathic pain due to physical damage to the neurons from malalignment of joints, trauma from falls, and surgery. V.H.'s description of her OA knee pain is consistent with nociceptive pain, most likely somatic in nature.

Clearly, the pain V.H. is describing in her feet is PDN. She is complaining of burning pain and dysesthesias, and a cold sensation at night. She has allodynia (pain caused by an innocuous stimulus) and hyperalgesia (increased pain in response to a noxious stimulus), which indicates peripheral and/or central sensitization. She has neuropathic damage in her lower extremities as indicated by decreased sensation with monofilament testing, nerve conduction velocity, and decreased reflexes. She likely also has some degree of peripheral vascular disease as evidenced by reduced hair growth on toes and diminished peripheral pulses. The combination of PDN and peripheral vascular disease is the pathogenesis of foot and leg ulcers in patients with diabetes. Management of PDN begins with improved glycemic control, which has been shown to reduce the incidence and slow the progression of neuropathy.

## **Treatment Plan for V.H.**

An individualized therapeutic goal should be established for patients in pain based on their desired outcomes. For example, V.H. has stated several functional goals, including the ability to remain independent in her own home, to grocery shop by herself, and move about her house and patio to garden. She is also concerned about the meaning of the foot pain (possible amputation). The patient may indicate a pain severity rating that he or she would find acceptable (e.g., pain of 4 or less with movement, less than 2 at rest [on a 0 = no pain, 10 = worst imaginable pain scale]), but the impact of pain on their activities of daily living is the more important therapeutic goal.

The management of OA pain is described in detail elsewhere in this book, and is summarized here. The American Pain Society published guidelines for managing pain in OA, rheumatoid arthritis, and juvenile chronic arthritis in 2002. Unfortunately, there is no cure for OA; however, nonpharmacological interventions, education, lifestyle changes and analgesics can significantly improve quality of life for patients with OA.

The American Pain Society guidelines advocate patient education, weight loss, physical exercise, cognitive-behavioral strategies, assistive devices, and surgery as nonpharmacological interventions. If educational interventions and lifestyle changes are insufficient to control pain, the guidelines advise use of acetaminophen up to 4 g/day for mild pain (particularly if the patient has no discernable inflammation) or COX-2 selective therapy for moderate to severe pain or inflammatory pain. Of course, given recent developments associating increased cardiovascular outcomes with COX-2 selective therapy,

patient appropriateness must be carefully considered. Serial trials of NSAID therapy (nonselective or COX-2 selective, as appropriate) should be implemented until an effective regimen is found. If a nonselective NSAID is used, the patient may require addition of a cytoprotective drug such as a PPI or misoprostol.

If these interventions do not achieve the therapeutic goals, additional therapies can be considered, such as intra-articular steroid injections, intra-articular hyaluronic acid injections, topical capsaicin cream, and use of glucosamine and chondroitin. If the patient's pain has a neuropathic component, an adjunctive analgesic is appropriate, such as an AED or TCA.

For patients who have not achieved the desired therapeutic outcome despite appropriate treatment, chronic opioid therapy is indicated. In general, this is administered as a single-ingredient drug (e.g., morphine and oxycodone) as an oral long-acting dosage form once or twice daily. An immediate-release opioid can be prescribed for moderate to severe breakthrough pain. Attention to the bowels is critical when starting a patient on opioid therapy; a bowel regimen will most likely be required to prevent opioid-induced constipation.

In the case of V.H., patient education and lifestyle changes (such as losing weight) are appropriate recommendations. It is not advisable for V.H. to use a heating pad, given her history of diabetes mellitus and the potential for tissue damage due to peripheral vascular disease. Because V.H. has significant pain, her health care provider elected to begin pharmacological therapy at the same time. Because no overt inflammation is noted, it was decided that V.H. should begin acetaminophen 1000 mg 4 times/day (or 1300 mg every 8 hours with an oral extended-release formulation). This intervention was moderately successful, but pain eventually returned. V.H. elected to add glucosamine sulfate 1000 mg/day, and achieved an acceptable level of pain control. After several months, however, pain recurred and impaired V.H.'s quality of life. After discussing the pros and cons of therapy with V.H., her health care provider started therapy with a COX-2 selective drug, titrated to the maximum dose. V.H. has no history of cardiovascular disease, but she was concerned about GI upset.

V.H. was unable to lose any substantial amount of weight and, after several successful years of therapy with a COX-2 selective NSAID, the pain became more severe. Her prescriber appropriately ordered oxycodone 2.5 mg every 4 hours as needed to establish the lowest effective total daily dose of oxycodone. A total daily dose of 20 mg oxycodone enabled the patient to resume her activities of daily living; therefore, opioid therapy was switched to oral, long-acting oxycodone, 10 mg every 12 hours, with 2.5 mg as needed for breakthrough pain. V.H. was also instructed to take a senna/docusate combination tablet 2 times/day to prevent constipation.

Management of V.H.'s PDN is discussed in the next section.

# Painful Diabetic Neuropathy

Diabetes mellitus is defined by the American Diabetes Association as “a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.” Over time, people with diabetes are subject to nerve damage throughout the body, resulting in significant morbidity and mortality. Painful diabetic neuropathy is one example of a peripheral neuropathic pain state that is frequently mismanaged.

## Pathophysiology

Diabetic neuropathy affects sensory, autonomic, and motor neurons of the peripheral nervous system, rendering practically every type of nerve fiber in the body susceptible. Patients with either type 1 or type 2 diabetes mellitus are at risk for the cardiovascular, GI, and sensorimotor complications of peripheral neuropathy.

There are several ways to classify diabetic neuropathy. When we refer to PDN we are referring to the chronic excruciating, refractory pain of sensorimotor neuropathy. Chronic sensorimotor neuropathy is the most common form of diabetic neuropathy and is often described as distal symmetrical sensorimotor polyneuropathy; it begins distally in the arms and legs, is symmetrical in nature, and affects multiple nerve fibers.

Epidemiologic research has shown the prevalence of diabetic neuropathy to be 30% in hospitalized patients and 20% in community patients. An older study that is frequently cited reported that about 7% of patients had neuropathy at the time they were diagnosed with diabetes and about 50% had neuropathy after 25 years of having the disease. Neuropathy associated with pain occurs in about 10% of those affected by neuropathy; therefore, about 4–5% of all patients with diabetes will have PDN.

The most significant risk factor for developing diabetic neuropathy is sustained hyperglycemia. Research has shown that improved blood glucose control reduces the odds; the Diabetes Control and Complications Trial disclosed an annual incidence of diabetic neuropathy of 2% in the conventionally treated group of patients. The intervention group had blood glucose control closer to nondiabetic physiology and an annual diabetic neuropathy incidence of 0.56%. The importance of good blood glucose control cannot be overemphasized for minimizing all diabetes-related complications.

Additional risk factors for PDN include duration of diabetes, patient age, cigarette smoking, alcohol consumption, hypertension, height (taller patients are at higher risk), and hypercholesterolemia.

The pathogenesis of PDN is not completely understood, although there are several theories in this likely multifactorial process. The metabolic theory proposes that intracellular hyperglycemia in nerves (which do not require insulin for glucose uptake) results in saturation of the

**Table 1-6. Stages of Diabetic Peripheral Neuropathy**

Stage of Neuropathy	Characteristics
No neuropathy	No symptoms or signs
Clinical neuropathy	Burning, shooting, stabbing pains with or without pins and needles; increased at night; absent sensation to several modalities; reduced/absent reflexes
Chronic painful	Severe symptoms as above (hyperesthesia common), may follow initiation of insulin in poorly controlled diabetes, signs minor or absent
Acute painful	Numbness/deadness of feet or no symptoms, painless injury, reduced/absent sensation, reduced thermal sensitivity, absent reflexes
Painless with complete/partial sensory loss	Numbness/deadness of feet or no symptoms, painless injury, reduced/absent sensation, reduced thermal sensitivity, absent reflexes
Late complications	Foot lesions, neuropathic deformity, nontraumatic amputation

Reprinted with permission from Blackwell Publishing. Boulton AJM, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med* 1998;15:508–14.

glycolytic pathway. Excess glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose results in decreased sodium/potassium-adenosine activity, reduced nerve myoinositol, impaired axonal transport, and structural breakdown of the nerve, which all leads to slowed conduction velocity.

The vascular theory describes how endoneurial ischemia develops due to increased vascular resistance secondary to hyperglycemic blood. The formation of advanced glycosylation end products also contributes to capillary damage, inhibition of axonal transport and sodium/potassium-triphosphatase activity, and axonal degeneration.

Other potential mechanisms in diabetic neuropathy include impaired production and transport of nerve growth factor, lack of normal expression of laminin (a glycoprotein that promotes neurite extension), and the development of autoimmune neuropathy.

## Assessment

Diabetic neuropathy is insidious in onset and is present in about 10% of patients at the time of diagnosis of type 2 diabetes mellitus. Although practitioners recognize the painful complaints associated with PDN, the damage generally develops slowly over time as a painless loss or change of sensation that can be detected and quantified only by clinical testing.

There have been several proposed staging systems for diabetic neuropathy. A consensus meeting of an international group of experts in diabetic neuropathy developed guidelines for managing diabetic peripheral neuropathy and agreed on clinical stages as shown in Table 1-6.

Clinical presentation of chronic sensorimotor neuropathy includes several classic signs and symptoms. Patients complain of pain and paresthesia, such as burning, tingling, aching, cold sensation, lancinating (sharp) pain like walking on glass, numbness, or pain from normal touch (allodynia). Patients may have dysesthetic complaints such as “buzzing” or “like bugs crawling.” Pain or unpleasant sensations may be present constantly, day and night, or may be noticeable primarily at bedtime. The pain may adversely affect quality and quantity of sleep.

Patients also complain of negative symptoms of sensory loss, such as inability to feel, identify, or manipulate smaller objects. Patients may lose ability to judge temperature or sense painful stimuli. Patients may also report unsteadiness in walking, and should use a night light to prevent falls at night. Patients with PDN frequently are depressed and/or anxious.

Physical signs seen on clinical examination usually include a symmetrical sensory loss to all modalities in a stocking-glove distribution (see Figure 1-4). Ankle reflexes may be reduced or absent, and knee reflexes may be absent. Motor weakness is unusual, although small muscle wasting may be seen in more severe cases. A simple handheld device that can be used to screen for neuropathic signs is the Semmes-Weinstein monofilament. The filament assesses pressure perception when gentle pressure is applied to the handle sufficient to buckle the nylon filament. The most commonly used is the 10-g pressure monofilament; sensitivity with this device ranges from 86% to 100%. Other useful instruments in the neuropathy examination include a tuning fork and instruments to perform tactile circumferential discrimination (e.g., 2-point discrimination). More sophisticated testing can be performed with Quantitative Sensory Testing (QST), which assesses vibration, thermal and pain thresholds in patients with diabetes. Whole nerve electrophysiologic procedures (such as nerve conduction velocity or electromyography) may be useful in detecting the onset and progress of PDN.

With disease progression, loss of innervation can lead to atrophy of essential pedal muscles, causing deformities such as hammertoes and predisposing the patient to callus formation and ulceration. Patients with diabetes generally have peripheral vascular disease, placing them at high risk for developing a diabetic foot ulcer, which is responsible for 85% of lower extremity amputations in patients with diabetes.

## Management

The therapeutic goal in managing PDN is to prevent, or at least delay, progression to greater symptom severity. Achievement of the patient’s functional goals is also important, such as the ability to sleep throughout the night without being awakened by the pain.

Several research trials have clearly demonstrated that maintaining near-normal glycemia prevents the development of PDN and retards its progression as assessed electrophysiologically. These studies include the Diabetes

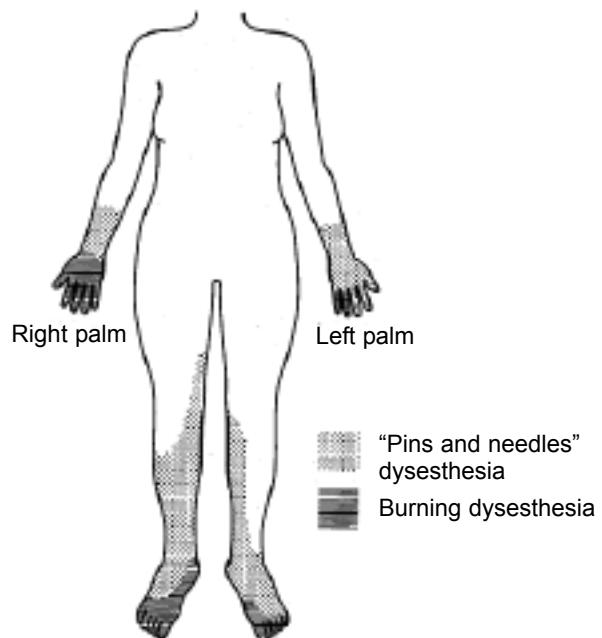


Figure 1-4. Painful peripheral neuropathy.

Reprinted with permission from Elsevier. McCaffery M. Selected pain Problems In: McCaffery M, Paser C, eds. Pain Clinical Manual, 2nd ed. St. Louis: Mosby, 1999:577.

Control and Complications Trial, the United Kingdom Prospective Diabetes Study, the Stockholm Diabetes Intervention Study, the Oslo Study, and the Kumamoto Study. Current recommendations for glycemic control from the American Diabetes Association include a hemoglobin A1c less than 7.0%, preprandial plasma glucose 90–130 mg/dl, and postprandial plasma glucose less than 180 mg/dl. Other groups recommend even tighter blood glucose control, such as hemoglobin A1c less than 6.5%. Other therapies continue to be investigated as potential interventions to prevent the onset or modify the progression of PDN, such as aldose reductase inhibitors, antioxidants, gamma-linolenic acid treatments, neurophins, glycation inhibitors, protein Kinase C (superfamily of 12 isoenzymes) inhibitors, and vasodilators. Clinical outcomes with these disease-modifying drugs have been disappointing to date, but remain a critical focus of interest for the future.

Current drug therapy interventions used in managing PDN have no effect on the progression of the disease; rather, they are used for symptomatic management. Gabapentin has quickly risen to the top of the list of drug therapy options to treat PDN due to its effectiveness and tolerability. Compared with placebo, gabapentin provided statistically superior pain relief and clinically significant improvement in global impression scales on quality of life assessments. When compared with amitriptyline, previously considered to be the gold standard in treating PDN, gabapentin provided equivalent pain relief with greater tolerability. A recent review of all clinical trials of gabapentin for

neuropathic pain concluded that doses of 1800–3600 mg/day were effective, with a more tolerable adverse effect profile than the TCAs.

Six placebo-controlled trials have demonstrated the effectiveness of the TCAs in the treatment of PDN. Desipramine, imipramine, amitriptyline, and clomipramine have the greatest efficacy. Although many practitioners think of amitriptyline as the TCA of choice, this drug causes the highest incidence of adverse effects among the TCAs. Desipramine has been shown to be equally effective, with greater tolerability. Clomipramine has demonstrated efficacy equivalent to desipramine. It is unfortunate that nortriptyline has not been compared head-to-head with amitriptyline, but clinical experience has shown nortriptyline to be a reasonable option. Advantages with the TCAs include low cost, 1 time/day dosing, and a beneficial effect on insomnia and depression. Benefits must be weighed against adverse effects.

There are some other antidepressant drugs and AEDs that can be considered. Extended-release venlafaxine 150–225 mg/day has been more effective than placebo or extended-release venlafaxine 75 mg/day in treating PDN. A smaller trial that was not blinded or placebo-controlled also showed significant pain reduction in a small series of patients with severe sensorimotor neuropathy. Citalopram and paroxetine also showed a beneficial effect in treating PDN.

Duloxetine is the only adjunctive analgesic that has an approved label indication by the FDA for treating PDN. Per the package insert, duloxetine was evaluated in 791 patients with PDN. Treatment with duloxetine 60 mg 1 or 2 times/day showed significant improvement in pain scores (greater than 50% reduction in pain scores from baseline). About 14% of patients receiving duloxetine for PDN discontinued therapy due to adverse effects versus 7% of placebo-treated patients. The most common causes for discontinuation were nausea, dizziness, somnolence, and fatigue. Additional adverse effects reported by 5% or more of patients who continued therapy and occurred at a rate of at least twice that seen in the patients who received the placebo included dry mouth, constipation, decreased appetite, and increased sweating. Clinical trials comparing the effectiveness of duloxetine to gabapentin, venlafaxine, or TCAs, plus additional clinical experience, will provide greater insight as to the role of this adjunctive analgesic in managing PDN.

Extended-release bupropion has been more effective than placebo in treating neuropathic pain of mixed etiology, but more than 50% of patients receiving bupropion experienced significant adverse effects.

As discussed above, gabapentin is a first-line intervention in the treatment of PDN. First-generation AEDs have demonstrated efficacy in treating PDN, but adverse effects limit clinical utility. Oxcarbazepine is likely preferable to carbamazepine; one small open-label trial showed this drug to be effective in treating PDN, with drowsiness and dizziness as primary adverse effects. Lamotrigine has demonstrated effectiveness and good tolerability in patients with PDN; one-third of patients

reported the drug was highly efficacious. The risk of toxic epidermal necrolysis remains a concern with lamotrigine therapy.

A relatively new treatment shown to be efficacious in treating PDN is transdermal lidocaine. Using a more flexible dosing schedule than the FDA-approved dosing strategy for PHN, researchers showed that applying up to four patches for an 18-hour period (then off for 6 hours) reduced pain by 30% or more in two-thirds of patients studied. Pain interference measures were also significantly improved, and the drug was well tolerated. Because the patch may move during walking when applied to the soles of the feet, some practitioners recommend applying the patch at bedtime. Many patients with PDN also experience increased pain at night, which is best treated with bedtime application.

Other viable options to treat PDN include tramadol and opioids. Tramadol is effective in milder pain, but requires more frequent dosing than oral long-acting opioids. Tramadol was shown to have a modestly beneficial effect in treating neuropathic pain, with doses in the range of 200–400 mg/day. Nausea and constipation developed in more than 20% of patients, and headache and dyspepsia occurred more frequently with tramadol than with placebo. Tramadol is a reasonable option to add to the analgesic regimen if pain is not acceptably controlled with adjunctive drugs.

Opioids have been examined in the treatment of a variety of neuropathic pain conditions with good success. Levorphanol was useful in treating a variety of peripheral and central neuropathy pain states, and oral long-acting oxycodone was evaluated in two trials of PDN. Adverse effects seen in these clinical trials are those expected with opioid therapy: constipation, somnolence, nausea, dry mouth, and dizziness. As with tramadol, opioids are an appropriate option as add-on therapy with other adjunctive analgesics to treat PDN or as monotherapy when other therapeutic options are not feasible or successful. As discussed earlier, physical dependence is expected with opioid therapy, and should not prevent their use to treat PDN.

When selecting an adjunctive drug for PDN, several patient- and drug-related variables must be considered. After optimizing glycemic control, for mild to moderate pain that is primarily causing sleep disturbance, a TCA may be beneficial (if other adverse effects are tolerated). If the patient has concurrent anxiety and/or depression, higher doses of TCAs would be required; therefore, duloxetine or venlafaxine may be preferable due to better tolerability. For moderate to severe pain or pain not accompanied by insomnia or depression, gabapentin is a good choice. If the pain is mostly localized, transdermal lidocaine is a reasonable option. Because most patients achieve only 30–40% pain relief with any one drug, a second drug added to the regimen is reasonable. Tramadol and opioids are options, either dosed on a time-contingent basis, or on an as-needed basis for more severe breakthrough pain.

In the case of V.H., she describes pain that is classic for PDN. She is anxious about her pain situation, but not clinically depressed. Because she complains of insomnia due to the pain, and has no other risk factors that would contraindicate TCA therapy, she is started on desipramine 10 mg at bedtime. She tolerates this dose, and desipramine is increased to 25 mg in 5 days. After about 10 days, she begins to appreciate a lessening of the pain. The dose is increased to 50 mg, and then 75 mg, where she achieved acceptable pain control.

Monitoring patient response to analgesic therapy is driven by the previously established therapeutic goal. The patient determines an acceptable pain rating (best, worst, average) and, more importantly, the ability to perform pain-interfering activities (improved quality of sleep, activities of daily living) and improved mood and affect. It is useful to encourage patients to maintain a pain diary to assess therapeutic response. A pain diary allows the patient to keep a log of drugs taken for the pain, pain severity rating before and after analgesic administration, and comments on his or her ability to perform activities of daily living. Physical assessment is important in terms of both positive and negative sensory findings. Blood glucose control should continue to be assessed, and maintained as close to euglycemia as is feasible.

Patient education is important with PDN. Patients need to understand what PDN is, how it occurs, symptoms of peripheral neuropathy, and treatment options. There is at present no treatment used to reverse PDN, but improved blood glucose control will help delay disease progression. Patients should be counseled on the importance of trying to prevent injuries such as burns or cuts (including those that result from inappropriate foot care). Because peripheral vascular disease frequently accompanies diabetic neuropathy, patients need to understand that they might not recognize an injury or infection until it develops into a poorly healing ulcer. Patients need to inspect skin on their feet and lower legs regularly, and see a podiatrist or other health care provider for managing calluses, sores on the skin, or other abnormalities in skin appearance, temperature, or sensation. Patients should be counseled to limit alcohol ingestion and quit smoking, as these factors may contribute to neuropathy development.

## Post-herpetic Neuralgia

Post-herpetic neuralgia is the most common and debilitating consequence of herpes zoster (shingles), which is the clinical manifestation of reactivated varicella zoster infection. Herpes zoster is one of the most common neurologic diseases in the United States, affecting about 500,000 people annually, with a lifetime prevalence as high as 20%.

### Pathophysiology

After the initial infection of chickenpox resolves, the varicella zoster virus stays in the body in a dormant state, residing in the neural ganglia. For up to 20% of patients, the virus reactivates and travels along sensory nerves to the skin's surface and causes herpes zoster. Risk factors for

reactivation of the virus include advanced age and conditions that decrease cellular immunity such as systemic illness or infection, stress, and malignancy (particularly lymphoma). A typical scenario is acute herpes zoster developing in an older adult who recently suffered a major life event, such as surgery, major illness, or a significant stress such as death or illness of a loved one.

Initially, patients describe a painful, dysesthetic prodrome, followed within a few days by a unilaterally distributed vesicular rash that most commonly affects thoracic and cranial dermatomes. Healing of this rash may take up to 1 month. For some patients, the pain that emerges with presentation of the rash persists; this condition is known as PHN. Although the definition varies, PHN is generally considered to be present when pain persists more than a month after eruption of the acute zoster rash and to be chronic when the pain persists for at least 3–6 months.

Risk factors for developing PHN include advanced age, with a marked increase in incidence after age 50. For example, the incidence of PHN is about 27%, 47%, and 73% in patients aged 55, 60, and 70 years, respectively. Older adults are more likely to experience PHN for a longer time and with greater severity than younger patients. Patients who experience severe pain, a severe rash, fever, and inflammation during the prodromal phase are at increased risk of developing PHN. Overall, about 10–20% of patients with herpes zoster will develop PHN, although literature estimates range from 4.5% to 47%.

Acute herpes zoster develops when cellular immunity to varicella decreases. Dormant virus particles that persist within affected sensory ganglia replicate and spread to the dorsal root, into the dorsal horn, and through the peripheral sensory nerve fibers down to the level of the skin, which leads to inflammation of the skin, hemorrhage, immune response and destruction of peripheral and central neurons and their fibers. Neuronal degeneration results in both peripheral and central sensitization, which is likely what causes PHN. Peripheral sensory fibers that survive this insult become hyperexcitable and begin to fire at lower thresholds and even spontaneously. Increased sensory fiber excitability is likely due to inflammation, increased expression of sodium channels and adrenergic receptors, and “sprout” formation at the damaged nerve tip. In response to this peripheral sensitization, dorsal horn neurons in the spinal cord become more responsive, resulting in central sensitization. If peripheral sensory fiber destruction is extensive, central processes of surviving axons may develop abnormal connections within the spinal cord, causing spontaneous pain and/or allodynia.

### Assessment

The most common sites for herpes zoster and PHN are the scalp and forehead. This presentation signals thoracic involvement, and ophthalmic involvement from the trigeminal nerve; therefore, an ophthalmic evaluation should be performed to assess and treat possible ocular involvement. Less commonly, herpes zoster and PHN may occur in the neck, arms, low back or legs, representing involvement of cervical, lumbar, or sacral dermatomes. PHN pain may involve several dermatomes, or be limited to several focal areas within the dermatome affected by the

herpes zoster rash. Some patients may have pain in an area that exceeds that of the original rash; this is likely due to central sensitization. Patients use a variety of terms to describe PHN, including burning, raw skin, sharp, electric-like, deep aching, and freezing cold. The vast majority of patients complain of dynamic allodynia. Abnormal itching may also be a complaint. Some patients may experience decreased muscle tone or weakness in the affected region.

On examination, the painful area may reveal a deep white discoloration and scarring in areas where the rash was severe. There are no consistent diagnostic sensory examination findings with PHN; patients have varied sensory examinations including areas of sensory deficit and/or allodynia and hyperalgesia.

The diagnosis of PHN is straightforward: a history of acute herpes zoster and continued pain in the affected area. Rarely, a patient will have characteristic PHN pain without a history of zoster rash; in this case, serologic studies can be used to confirm the diagnosis.

Post-herpetic neuralgia generally resolves in most patients over time. If a patient has had PHN for a year or more, it is unlikely that the pain will spontaneously resolve. Persistent pain of this nature can have a significant adverse effect on quality of life, including psychological and social well-being and physical functioning.

## Management

An important goal in managing acute herpes zoster infection is to limit severity, which will reduce the risk or severity of PHN. If PHN develops despite early intervention, the goal is to treat the pain, allowing enhanced quality of life.

Limiting the severity of the acute herpes zoster infection will likely spare neural damage, which should reduce acute pain and subsequent postherpetic pain. Presently, the most effective way to accomplish this goal is with an antiviral drug. Many clinical trials have shown that administering an antiviral such as acyclovir, famciclovir, or valacyclovir within 72 hours of zoster rash onset significantly reduces pain that accompanies the rash, and reduces the severity and duration of PHN.

Nerve blocks administered during acute herpes zoster have not been shown to work as “preemptive analgesia” for PDH, although this intervention may be warranted to treat severe pain associated with acute herpes zoster. Some research suggests that administering an adjuvant analgesic preemptively may be beneficial. One small study evaluating the use of amitriptyline during acute herpes zoster infection showed some protection against PHN. Additional clinical trials are required to confirm these findings.

Adjunctive analgesics are the mainstay of treatment in PHN. As with other neuropathic pain states, PHN is generally refractory to traditional analgesic therapy, and adjuvant therapies may not completely relieve pain as single-drug therapy. Preferred therapies include transdermal lidocaine, gabapentin, opioids, and TCAs (although their use is limited by adverse effects).

The topical lidocaine transdermal patch was the first analgesic to receive a labeled indication by the FDA for treating PHN. Building on data that found 5% topical lidocaine gel to be effective, the 5% transdermal lidocaine patch was also efficacious. In a double-blind, multiple crossover, vehicle-controlled study of 35 patients with PHN, 12-hour application of up to three patches significantly reduced pain intensity compared with no treatment or vehicle patch. Additional research has shown the lidocaine patch to be efficacious on a long-term basis and that discontinuation is strongly correlated with recurrence of the pain. Studies also showed that this product enhances quality of life of patients with PHN. In a large (n=332), open-label, multicenter, 28-day study, 74% of patients with PHN reported improvements in quality of life within the first week of treatment. About 3% of the lidocaine is systemically absorbed from the patch, and adverse effects are minimal; the most common adverse effect is a localized rash in 14% of patients studied, which was considered to be mild. The approved dose is up to three patches applied for a 12-hour period, followed by a 12-hour drug-free interval. Some research suggests that four patches applied for up to 24 hours on 3 consecutive days produces analgesia without systemic adverse effects or edema. The patches can be cut and applied directly to sites of pain, providing directed analgesia. Although the length of therapy is determined by patient need, some patients have reported using the lidocaine patch for more than 8 years without evidence of tolerance or increased adverse effects.

Although a variety of AEDs are efficacious in treating various pains of neuropathic origin, gabapentin has the best data to support this indication and is the only systemic drug approved for treating PHN. Gabapentin was approved for this indication based on two large (563 patients between the two trials), randomized, placebo-controlled trials. In one study, patients were titrated to the maximum tolerated dose (up to 3600 mg/day) or placebo. Gabapentin-treated patients achieved significantly greater pain relief and improvement in sleep. The second study allowed gabapentin doses of 1800 or 2400 mg/day and had similar results. Gabapentin is well-tolerated; patients generally develop tolerance to the adverse effects such as somnolence, dizziness, and ataxia.

Opioids have been evaluated in numerous clinical trials for managing PHN. Controlled-release oxycodone has been used with significant benefit in treating patients with intractable PHN pain, with pain control maintained for up to 6 months without developing tolerance to the therapeutic effect. Levorphanol also provides significant relief in treating a variety of peripheral and central neuropathic pain conditions, including PHN. In the levorphanol study, higher doses resulted in greater pain relief, equivalent to that reported with gabapentin and TCAs. A recent, randomized, double-blind, crossover trial (n=50) evaluated the comparative efficacy and tolerability of two opioids (slow-release morphine and methadone) and two TCAs (nortriptyline and desipramine) in managing PHN. Morphine reduced mean pain scores by 2.2 points, methadone by 1.2, nortriptyline by 1.2, and desipramine by

Katz NP, Gammaioni AR, Davis MW, et al. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. Pain Med 2002;3:324-32.

1.6. Morphine resulted in significantly greater pain relief than nortriptyline ( $p=0.004$ ); the analgesic efficacy of methadone was equivalent to the two TCAs. The TCAs also caused significant reduction in cognitive functioning, which was not reported with either opioid. Initially, a greater percentage of patients discontinued therapy in the opioid arms, although the majority of patients preferred opioid therapy to either TCA, likely due to enhanced pain relief.

The TCAs have been studied at length in managing PHN, particularly amitriptyline. Using an average daily dose of 75 mg at bedtime, amitriptyline had a response rate of 47–66%. Similar results have been seen with nortriptyline and desipramine. The drawback to TCA therapy is the side effect profile, including anticholinergic effects and postural hypotension. Older adults are particularly susceptible to these adverse effects, including increased risk of glaucoma, falls due to dizziness, postural hypotension, and sedation and cardiac dysfunction. Other antidepressant drugs have demonstrated efficacy in treating other neuropathic pain states, but there is little literature supporting their use in PHN.

A variety of other interventions have been tried, primarily anecdotally, for managing PHN. One study of 277 patients showed promising results with weekly intrathecal injections of methylprednisolone (60 mg) with lidocaine (3 mg), although safety concerns, such as aseptic meningitis, adhesive or calcific arachnoiditis, and spinal pachymeningitis, have been raised with this approach. A few uncontrolled studies of tizanidine treatment have shown effectiveness in PHN. Capsaicin was evaluated in patients with PHN with mixed results. Some studies showed improvement in pain and functional status, whereas others did not. Adverse effects, including burning on application, limit acceptability to patients.

Although no clear-cut treatment algorithm exists for the treatment of PHN, both lidocaine patches and gabapentin are preferred initial therapies. The lidocaine patch is probably the most reasonable option to begin with, given its efficacy, ease of administration, safety, and tolerability, which exceeds that of other therapeutic options. Opioids are also preferable to TCAs, although TCAs remain reasonable options, particularly the drugs with the least anticholinergic activity (e.g., nortriptyline and desipramine).

It is unlikely that a single drug will provide complete pain relief given the complex and frequently heterogeneous nature of PHN. If the patient does not achieve a satisfactory outcome with the initial selection (which is defined as at least a 33% reduction from baseline pain and improvement in functional status), systematic trials of other drugs should be instituted. If a patient is using the lidocaine patch with a partial response, it would be reasonable to add gabapentin as a second-line drug. If this regimen does not achieve the therapeutic goal, opioids or TCAs may be considered.

As mentioned above, psychological and behavioral interventions may be introduced at any time during therapy and are important for patients with refractory PHN.

Rehabilitation issues may need to be addressed by physical and occupational rehabilitation practitioners.

Monitoring response to therapies for PHN is similar to that described previously for PDN and should include the patient's pain rating and functional goals. Patients should be encouraged to maintain a pain diary and discuss progress with their primary care practitioner. Patient education is important with PHN and should begin immediately following diagnosis and before instituting therapy. Patients need to understand what is causing the pain and how this pain is different from more usual and customary pains they have likely experienced. Patients' expectations for pain relief should be explored and the issues and likely outcomes in treating complex neuropathic pain such as is seen with PHN should be explained.

## Low Back Pain

Low back pain is one of the most prevalent pain syndromes in the United States, and is one of the most common reasons patients visit health care practitioners. Unfortunately, the multifaceted nature of LBP contributes to the controversy surrounding treatment, and there is professional uncertainty about optimal treatment.

### Pathophysiology

Some disagreement exists about the classification of LBP as acute or chronic. Acute pain is generally considered to be pain that resolves within 6 weeks (patient pain-free before onset of pain), subacute if the pain lasts between 6 and 12 weeks, and pain that persists beyond 12 weeks is considered chronic.

In most cases, LBP does not receive an exact diagnosis. For this reason, generalized terms such as lumbar sprain/strain, mechanical back pain, and acute nonspecific/myofascial pain are used to describe LBP.

Back pain represents one of most commonly experienced pain syndromes by Americans. Between 70% and 85% of the population experiences back pain during their lifetime, and up to 45% suffer from back pain in any given year. Men and women are affected equally, most commonly between the ages of 30 and 50 years. The lifetime recurrence rate of LBP is up to 85%. About 25% of workers' compensation claims and 40% of sick leave episodes are related to back pain complaints. The cost from back pain to the United States economy in 1990 was estimated to be between \$50 and \$100 billion. Risk factors for LBP include heavy lifting, twisting, bodily vibration, obesity, and poor conditioning, although LBP is common in patients without these known risk factors.

Low back pain is most commonly due to musculoligamentous injuries and age-related degenerative processes in the intervertebral disks and facet joints. However, pain may originate from any of the spinal structures, including ligaments, facet joints, blood vessels, the vertebral periosteum, the paravertebral musculature and fascia, the anulus fibrosus, and spinal nerve roots. Other

Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 2002;59:1015–21.

common causes of LBP include spinal stenosis (narrowing of the central spinal canal or its lateral recesses) and disk herniation.

When considering the differential diagnosis of LBP, mechanical low back or leg pain represents 97% of cases. The vast majority of cases are lumbar strain (damage or tearing of a muscle) or sprain (damage to ligaments or a joint capsule). This usually indicates that there has been stretching of the ligaments or muscles beyond the usual range of motion, which leads to microscopic tearing. A herniated disk is also called a herniated nucleus pulposus; intervertebral disks may also rupture or prolapse. Disks that separate the vertebrae of the spine have an outer layer called the annulus fibrosus and an inner layer called the nucleus pulposus. A herniated disk refers to a protrusion of the nucleus pulposus through the anulus fibrosus as the result of trauma or degenerative changes. Spinal stenosis is usually caused by hypertrophic degenerative changes of the facets and thickening of the ligamentum flavum, resulting in a severely narrowed spinal canal. Far less common causes of mechanical low back or leg pain include osteoporotic compression fracture, spondylolisthesis (anterior displacement of a vertebra on the one beneath it), traumatic fracture, and congenital disease.

Nonmechanical spinal conditions represent about 1% of LBP cases and include pathologies such as neoplasia (e.g., multiple myeloma, metastatic carcinoma, lymphoma, leukemia, spinal cord tumors, retroperitoneal tumors, and primary vertebral tumors), infection (e.g., osteomyelitis, septic diskitis, paraspinous abscess, epidural abscess, shingles), inflammatory arthritis (e.g., ankylosing spondylitis, psoriatic spondylitis, Reiter's syndrome, inflammatory bowel disease), osteochondrosis, and Paget's disease of the bone. Visceral diseases may also cause referred pain, and represent about 2% of LBP cases. Examples include disease of pelvic origin (e.g., prostatitis, endometriosis, and chronic pelvic inflammatory disease), renal disease (e.g., nephrolithiasis, pyelonephritis, and perinephric disease), aortic aneurysm, and GI disease (e.g., pancreatitis, cholecystitis, and penetrating ulcer).

Radicular pain occurs along the distribution of a nerve root or primary nerve trunk. Radicular LBP arises from an injury to spinal nerve roots or due to ischemia or decreased blood flow to spinal nerves. Low back pain may also be neurogenic, arising from abnormalities in the CNS with damage to the sensory portion of the nerve.

Children less than 17 years of age with LBP usually have a definitive etiology and a different differential diagnosis. Children rarely complain of LBP unless it is persistent or limits their activities of daily living. One series evaluating 100 children with LBP showed 84 had an identifiable cause such as occult fractures, spondylosis (dissolution of vertebra) or spondylolisthesis, scoliosis or kyphosis, tumors, or infection. Therefore, children should be referred for more extensive work-up when LBP is present.

## Assessment

The United States Agency for Health Care Policy and Research, now renamed the Agency for Healthcare Research and Quality, published the first evidenced-based

guidelines for managing back pain in 1994, titled Clinical Practice Guideline: Acute Low Back Problems in Adults. These guidelines have not been updated since they were published; however, the Veterans Health Administration/Department of Defense has published a document titled Clinical Practice Guideline for the Management of Low Back Pain or Sciatica in the Primary Care Setting. The management algorithm from these guidelines is shown in Figure 1-5.

The assessment of a patient complaining of LBP includes a medical and surgical history, physical examination, and assessment for the presence of "red" and "yellow" flags. Red flags are signs that may indicate serious spinal pathology, and yellow flags are factors recognized as having an influence on long-term disease outcomes, and which may obscure assessment and treatment. The medical history should include the eight elements of symptom analysis discussed earlier (precipitating and palliating events, quality, region/radiation, severity, temporal, associated symptoms, and previous treatment or therapy). The nature of the complaint should be carefully clarified: Is it just pain, or is the pain accompanied by numbness, weakness and stiffness? When asking about the pain and any accompanying symptoms, the patient should indicate the percentage of low back and/or leg that are affected, and if the pain extends below the knee. If the leg is involved, is it one leg or both? Is the pain constant or intermittent? Patients should specifically be asked about any insidious or recent trauma. They should also be asked about limitations imposed by the condition (e.g., unable to work or sleep) and nature of physical demands of work, if applicable. It is useful to ask and document how long patients can sit, stand, and walk, and how much weight they can lift. A neurological history should be obtained, particularly bowel and bladder symptoms, weakness and presence of numbness, and presence of constitutional symptoms (e.g., fever, weight loss, and night pain). Medical history should include any previous spinal surgery with persistent pain, drug-seeking behavior or intravenous drug abuse, cigarette smoking, and history of immunosuppression (cancer, steroid use, and human immunodeficiency virus).

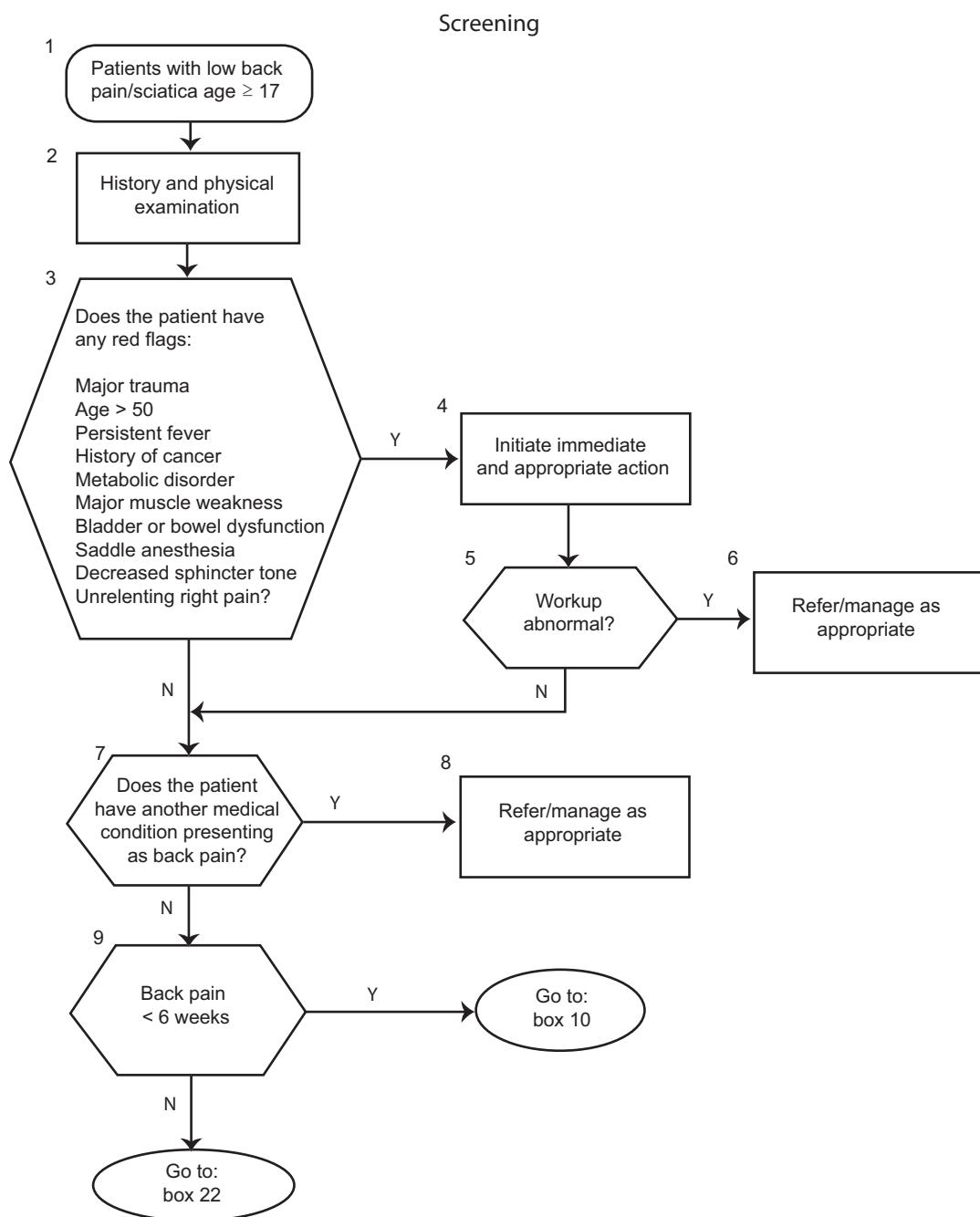
Mechanical LBP is pain associated with the mechanics of the back itself, such as muscle or tendon damage. This type of pain is associated with activity and causes significant superficial soreness or tenderness. Mechanical LBP generally does not radiate from the site of pain.

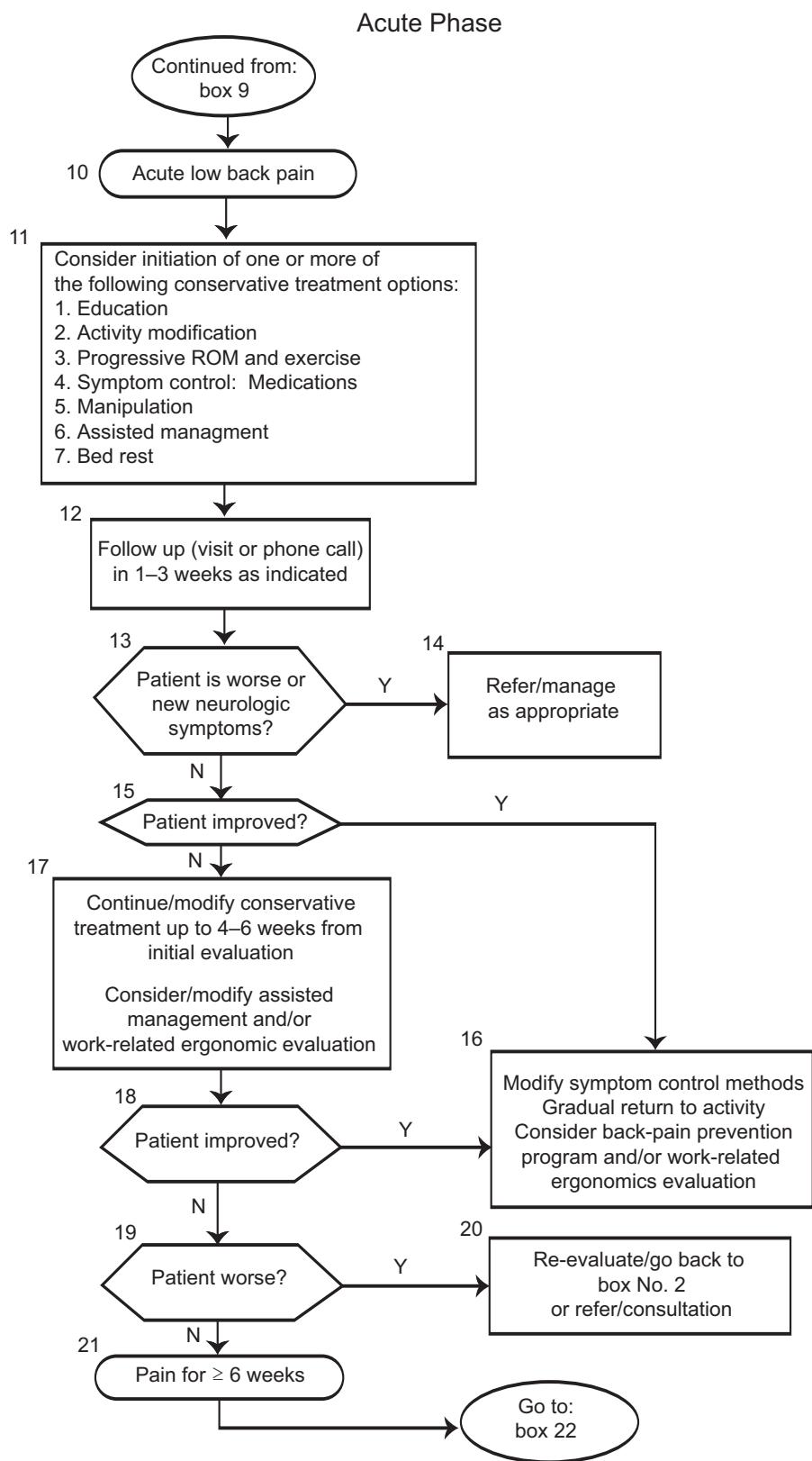
Radicular pain is generally present when patients complain of lancinating, shooting, sharp, and burning-type pain that frequently radiates to another area. Sciatica is a common form of radicular pain that causes radiating, shooting pain into the buttock and down the back of the leg. Neurologic involvement is also suggested when the patient complains of pseudoclaudication (leg pain after walking that mimics ischemic claudication). Leg pain in these situations is frequently associated with numbness or paresthesia. Sciatica due to disk herniation usually increases with cough, sneezing, or Valsalva maneuver. Patients with LBP with CNS damage may experience allodynia. Symptoms and prognosis for nonspecific back pain and nerve root pain are shown in Table 1-7.

Bowel or bladder dysfunction may be a symptom of severe compression of the cauda equina (known as cauda equina syndrome), which is a medical emergency caused by a tumor or a massive midline disk herniation. This is one of the red flags of back pain-related pathology, as shown in Table 1-8; patients with suspected cauda equina syndrome require an immediate consult with a spine surgeon.

A psychosocial and socioeconomic history of the patient should be obtained. Factors such as work status, typical job tasks, educational level, pending litigation, workers' compensation or disability issues, failed previous treatments, substance abuse, and depression have been

correlated with LBP. The patient should be screened for yellow flags, which are psychosocial factors that are indicative of long-term chronicity and disability with LBP. These include a negative attitude about the back pain, fear avoidance behavior and reduced activity levels, belief that passive treatment is preferred over active, a tendency to depression, and social or financial problems. The patient's attitudes and beliefs about LBP, illness behavior, the presence of psychological distress and depressive symptoms, diagnostic and treatment issues, and family and work factors should be explored.





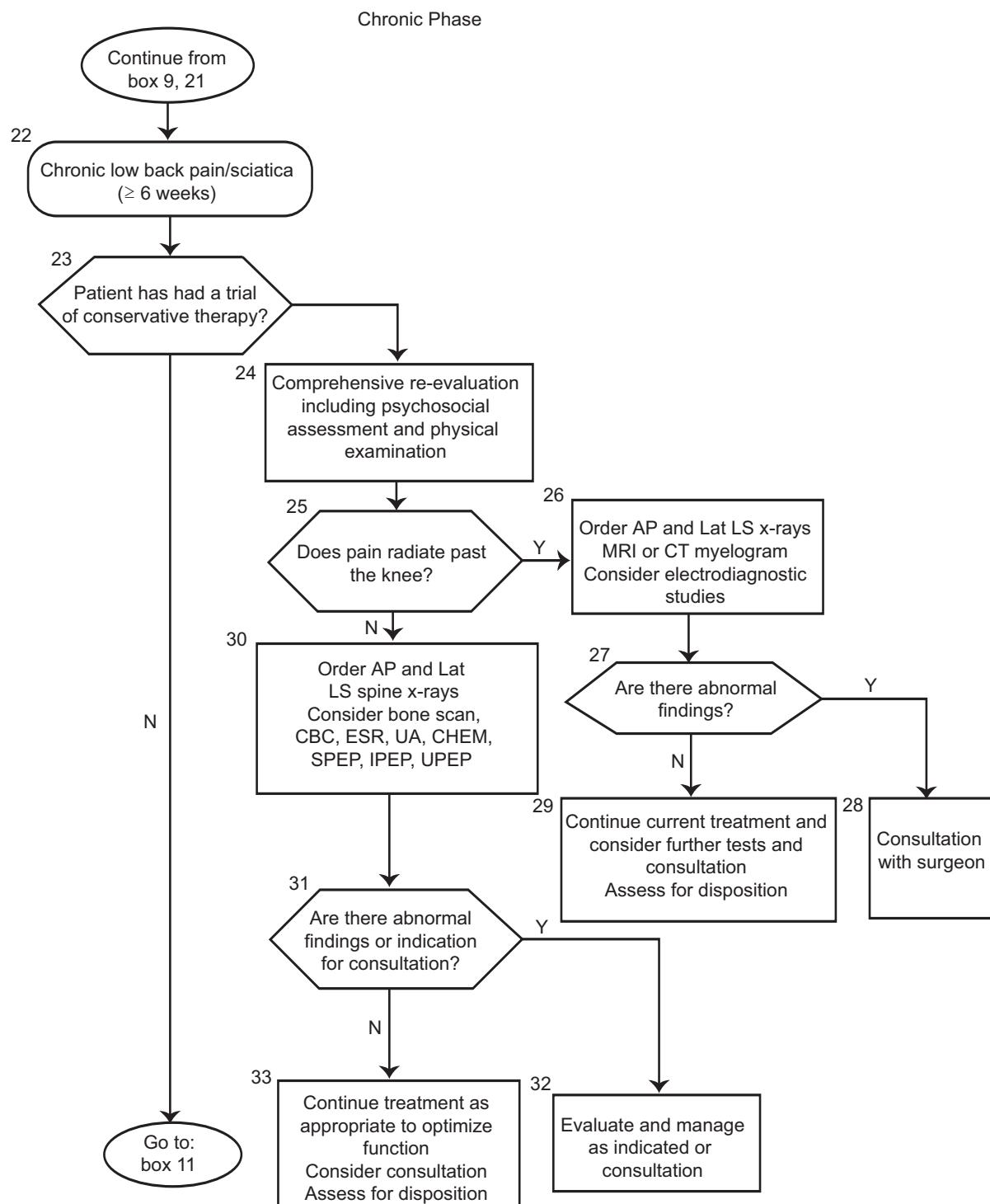


Figure 1-5. Management of low back pain or sciatica in the primary care setting.

AP = Anteroposterior; CBC = complete blood count; CHEM = chemistry; CT = computed tomography; ESR = erythrocyte sedimentation rate; IPEP = serum immunoelectrophoresis; Lat = lateral; MRI = magnetic resonance imaging; ROM = range of motion; SPEP = serum protein electrophoresis; UA = urinalysis; UPEP = urine protein electrophoresis.

National CPF Council. Low Back Pain or Sciatica in the Primary Care Setting. Washington, D.C.: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs, and Health Affairs, Department of Defense, November 1999. Office of Quality and Performance publication 10Q-CPG/LBP-99.

**Table 1-7. Symptoms and Prognosis for Nonspecific Back Pain and Nerve Root Pain**

Nonspecific back pain
Patient is 20–55 years old
Pain is located in the lumbosacral area (buttocks and thighs)
Pain presentation is mechanical and varies both with physical activity and time
Patient is generally well
Prognosis is good; 90% recovery from acute attack within 6 weeks
Nerve root pain
Unilateral leg pain worse than low back pain
Pain generally radiates to foot or toes
Numbness and paresthesia in the same distribution
Nerve irritation signs
Reduced straight leg raise reproducing leg pain
Motor, sensory, or reflex change
Limited to one nerve root
Prognosis is fair: 50% recover from acute attack within 6 weeks

National CPG Council. Low Back Pain or Sciatica in the Primary Care Setting. Washington, D.C.: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs, and Health Affairs, Department of Defense, November 1999. Office of Quality and Performance publication 10Q-CPG/LBP-99. Waddell G, McIntosh A, Hutchinson A, Feder G, Lewis M. Low Back Pain Evidence Review. London: Royal College of General Practitioners, 1999. Available at [http://www.chiro.org/LINKS/GUIDELINES/FULL/Royal\\_College/index.html](http://www.chiro.org/LINKS/GUIDELINES/FULL/Royal_College/index.html). Accessed September 12, 2005.

**Table 1-8. Red Flags for Other Back Pain-related Pathology**

Possible serious spinal pathology
Patient younger than 20 years or onset older than 55 years
Experience of violent trauma (e.g., fall or car accident)
Constant, progressive, or non-mechanical pain
Thoracic pain
Previous history of:
• Carcinoma
• Systemic steroids
• Drug abuse or HIV
Systemically unwell
Weight loss
Persisting severe restriction of lumbar flexion
Widespread neurological symptoms
Structural deformity
Cauda Equina Syndrome/Neurological Disorder
Difficulty with micturition
Loss of anal sphincter tone or fecal incontinence
Saddle anesthesia about the anus, perineum, or genitals
Widespread or progressive motor weakness in the legs or gait disturbance
Inflammatory Disorders
(Ankylosing spondylitis and related disorders)
Gradual onset before age 40
Marked morning stiffness
Persisting limitation of spinal movement in all directions
Peripheral joint involvement
Iritis, skin rashes (psoriasis), colitis, or urethral discharge
Family history

HIV = human immunodeficiency virus.

National CPG Council. Low Back Pain or Sciatica in the Primary Care Setting. Washington, D.C.: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs, and Health Affairs, Department of Defense, November 1999. Office of Quality and Performance publication 10Q-CPG/LBP-99. Waddell G, McIntosh A, Hutchinson A, Feder G, Lewis M. Low Back Pain Evidence Review. London: Royal College of General Practitioners, 1999. Available at [http://www.chiro.org/LINKS/GUIDELINES/FULL/Royal\\_College/index.html](http://www.chiro.org/LINKS/GUIDELINES/FULL/Royal_College/index.html). Accessed September 12, 2005.

The physical examination should include observation of posture, body habitus, stance, and gait. Regional back examination with range of motion testing of spine, hips, and lower extremities should be performed, as well as a straight leg raise and crossed straight leg raise. A complete neurologic examination is appropriate, including motor strength, muscle wasting, sensation, deep tendon reflexes, and specific reflexes, such as Babinski and clonus. Nerve root pain is suggested when unilateral leg pain is worse than LBP, the pain radiates below the knee, numbness and paresthesia is seen in the same distribution, the straight leg raise reproduces the leg pain, and the patient has localized neurological signs.

Some practitioners believe that radiology should be the primary diagnostic tool in LBP. However, several studies have demonstrated the questionable relationship between spinal abnormalities and patient complaints of LBP. In one study that was blinded and randomized, spinal computed axial tomography scans from 58 patients (52 patients with no history of LBP, six with known spinal disease) were reviewed by three neuroradiologists. Overall, 35% of the scans were found to be abnormal; however, 52 of 58 patients were asymptomatic. The most common abnormalities were herniated disk, facet degeneration, and stenosis. Another study found that herniated disks confirmed by magnetic resonance imaging were more strongly correlated to patients' perceptions about their work, such as occupational mental stress and job dissatisfaction, or other psychosocial issues such as depression, anxiety or marital problems, than complaints of back pain.

Acute LBP may become chronic, and patients with chronic LBP have a high incidence of depression. Chronic LBP is a leading cause of sick days lost from work, and some patients never return to work. Risk factors for LBP becoming chronic include previous history of LBP, regular work loss (due to LBP) in previous 12 months, radiating leg pain, reduced straight leg raising, signs of nerve root involvement, reduced trunk muscle strength and endurance, poor physical fitness, self-rated poor health, heavy smoking, psychological distress and depressive symptoms, disproportionate illness behavior, low job satisfaction, personal problems (e.g., alcohol abuse, marital problems, and financial problems), and ongoing adversarial medico-legal proceedings.

## Management

The goal in treating acute LBP is to relieve the symptoms, to recover from the acute attack with no residual chronic LBP or related disability, to maintain productivity, including ability to work, and to prevent recurring episodes of acute LBP. For patients with chronic LBP, the goal is to maximize ability to perform activities of daily living, including work, and to minimize risk of depression.

### Acute LBP

The management of acute LBP is multifactorial (see Table 1-9); the most important element is patient education. Specifically, patients need to be educated on risk factors for developing acute LBP, the usual course of back pain resolution, and red flags that may indicate serious pathology. Many patients believe acute LBP is an indication

**Table 1-9. Management of Low Back Pain or Sciatic in the Primary Care Setting**

Pharmaceutical Methods	Physical Methods	
Nonspecific LBP/Sciatica	Nonspecific LBP	Sciatica
<b>RECOMMENDED</b>		
Analgesics (e.g., acetaminophen or NSAIDs)	Manipulation (in place of drugs or a short trial if combined with NSAIDs)	
Muscle relaxants <sup>a, b, c</sup>		
Opioids <sup>a, b, c</sup>	Physical agents and modalities <sup>a</sup> (heat or cold modalities for home programs only)	Manipulation (in place of drugs or a shorter trial if combined with NSAIDs)
Corticosteroid epidural injection(s)		Physical agents and modalities <sup>a</sup> (heat or cold modalities for home programs only)
		2–4 days rest <sup>c</sup>
		Shoe insoles <sup>a</sup>

<sup>a</sup>Equivocal efficacy.<sup>b</sup>Significant potential for producing drowsiness and debilitation; potential for dependency.<sup>c</sup>Short course (few days only) for severe symptoms.

LBP = low back pain; NSAID = nonsteroidal anti-inflammatory drug.

National CPG Council. Low Back Pain or Sciatica in the Primary Care Setting. Washington, D.C.: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs, and Health Affairs, Department of Defense, November 1999. Office of Quality and Performance publication 10Q-CPG/LBP-99.

for prolonged bedrest when in fact most patients will not require bedrest at all, and if they do, it should not exceed 2 days. Although patients with acute LBP may be more comfortable if they temporarily limit or avoid specific activities known to increase stress on the spine, remobilization is an important goal. Spinal manipulation and massage may also be useful therapeutic interventions. The goal of pharmacological management of acute LBP is to allow the patient to remain as active as possible while awaiting spontaneous recovery and to permit participation in activities such as conditioning exercises. The most commonly used drugs in acute LBP include acetaminophen, NSAIDs, skeletal muscle relaxants, and opioid analgesics.

### Chronic LBP Management

As shown in Figure 1-5, the Department of Veterans Affairs/Department of Defense guidelines recommend confirming that patients with LBP that exceeds 6 weeks have received an adequate trial of conservative therapy. That being the case, the guidelines call for a comprehensive re-evaluation, including psychosocial assessment and physical examination. The practitioner should make sure no red or yellow flags are present; if they are, the patient should be referred for further evaluation (e.g., emergency room with red flags). It is known that social, economic, and psychological factors are more important than physical factors in affecting the symptoms, response to treatment, and long-term outcomes of patients with chronic LBP; therefore, observation of yellow flags and an appropriate referral is as important as observing red flags.

If the patient's pain radiates below the knee, this may be indicative of a neurologic problem that may benefit from surgical intervention. If surgery is not appropriate, or no pathology is noted, the patient may benefit from referral to a back specialist, a different specialist, or multidisciplinary therapy. For chronic sciatica that persists longer than 6 weeks, atypical chronic leg pain, or new or progressive neuromotor deficits, a neurology referral is appropriate. A rheumatology consultation would be appropriate to rule out inflammatory arthropathy, fibrositis/fibromyalgia, or

metabolic bone disease such as osteoporosis. A primary care sports medicine specialist may be helpful for other chronic LBP that is present for more than 6 weeks, chronic sciatica for more than 6 weeks, or recurrent back pain. For difficult workers' compensation situations, disability, or other work issues, a referral to an occupational medicine specialist should be considered. Multidisciplinary therapy represents a combination of exercises, education, and behavioral therapy, and is sometimes referred to as functional restoration. There is strong evidence that intensive multidisciplinary biopsychosocial rehabilitation with functional restoration improves function and moderate evidence that it reduces pain compared with outpatient nonmultidisciplinary rehabilitation or usual care. This type of intervention is generally expensive, and not always covered by third-party payers.

Intensive exercise reduces pain and improves functional status in patients with chronic LBP; however, adherence to a regimen of this nature is difficult. In addition, patients may require analgesic therapy to allow them to participate in such an exercise regimen and to enhance their functional ability. Unfortunately, there are no "magic bullets" in treating chronic LBP. Therapeutic options are the same as discussed in acute LBP—acetaminophen, NSAIDs, SMRs, and opioids plus adjuvant and miscellaneous drugs.

If time-contingent or as-needed acetaminophen is sufficient to control pain and improve functional status, most practitioners would agree that is appropriate. As of 2000, there were only five randomized, controlled trials evaluating the use of NSAIDs in chronic LBP. The methodologies are too diverse to allow a meta-analysis and include the following treatment comparisons: naproxen versus diflunisal versus placebo; diflunisal versus acetaminophen; diclofenac versus chiropractic manipulation versus physiotherapy; indomethacin versus oxamethacin; and piroxicam versus indomethacin. Results showed NSAIDs provided better pain relief than placebo although most trials were of short duration; withdrawal rates due to adverse effects ranged from 3% to 23%. There was no significant difference among the NSAIDs evaluated.

There is only one clinical trial evaluating an SMR for chronic LBP: tetrazepam (not marketed in the United States) versus placebo. There was a statistically significant difference between the two treatments; however, the trial lasted only 2 weeks and 7% of patients withdrew due to adverse effects. Most practitioners would agree that SMRs do not play a significant role in chronic LBP.

The prescribing of opioids is second only to NSAIDs for CNMP, and opioid use is gaining ground in managing chronic LBP. Chronic LBP is likely largely mechanical, which indicates nociceptive pain, but can frequently include a neuropathic component. Opioids represent a reasonable analgesic choice, as they are effective in both nociceptive and neuropathic pain. Although not a panacea, a recent review of 13 trials evaluating the use of opioids in managing chronic LBP showed that a variety of opioids (morphine, oxycodone, codeine, methadone, levorphanol; short- and long-acting; and oral and transdermal) result in significant pain relief. Opioid use is associated with developing adverse effects, but tolerance usually develops to these effects with the exception of constipation. The risk of drug abuse or psychological dependence was between 1% and 10%, highlighting the importance of screening patients for a possible history of drug abuse or drug diversion. One study compared naproxen versus set-dose oxycodone versus titrated oxycodone or titrated sustained-release morphine. The titrated opioids showed significantly less pain and improved mood and low risk of abuse. Tramadol (classified at best as a weak opioid or as a nonopiod) has also been beneficial, although some patients find it intolerable due to CNS or GI adverse effects. The two most important aspects of using opioids for CNMP such as chronic LBP are careful candidate selection, and assessment and documentation of therapeutic effect. For example, the practitioner should assess patient risk factors for substance abuse or diversion. These include a personal history of substance abuse or diversion, a family history of substance abuse problems, and significant psychopathology, particularly sociopathy. Substance abuse screening tool, such as the CAGE questionnaire or the Drug Abuse Screening Test, should be used. It is also appropriate to begin with the end in mind. Discuss the therapeutic goal with the patient, and be specific regarding functional improvement. Establish an expected timeline for improvement and a plan for titrating off the opioid if the goal is not achieved.

As described in the pathogenesis of LBP, both peripheral and central mechanisms play a role, particularly when there is a neuropathic component. Probable peripheral mechanisms include neurogenic spread of chronic inflammatory pain, peripheral hyperalgesia and allodynia, highly activated sodium channels, and ectopic neural triggering. These peripheral processes lead to the development and maintenance of central mechanisms such as neuronal hyperactivity, changes in membrane excitability and expression of new genes. This results in perpetuation of the pain perception in the absence of ongoing tissue injury. Furthermore, the idea that neuropathic LBP is present only in the face of radiculopathy has been put to rest; peripheral and central mechanisms give rise to aggravation of neural

structures other than the nerve root as well. Given these pathologies, it would be reasonable to consider use of adjunctive analgesics for managing chronic LBP.

Adjuvant drugs have been investigated for managing chronic LBP, particularly antidepressant drugs. A meta-analysis of nine randomized, controlled trials published between 1966 and 2000 evaluating the use of antidepressant drugs for chronic LBP was published in 2002. Although there were variations in study methodology, the conclusion was that antidepressant drug therapy has a small but significant effect compared with placebo in reducing chronic LBP. A small but not significant trend was observed in improving function in activities of daily living. Postulated mechanisms of action for antidepressant drugs in treating chronic LBP include relief of depression. In 6 of 7 studies reviewed that included patients who were depressed, depression improvement was statistically significant. However, an improvement in back pain and functioning was also seen in patients without depression, suggesting a different mechanism of action, likely due to neurotransmitter action. The TCAs were superior to the SSRIs, with the latter offering little benefit. Of importance, therapeutic gain must be weighed against adverse effects associated with TCA therapy. Doses used in these studies were equivalent to those used to treat depression; therefore, adverse effects were significant. More than 20% of patients studied experienced adverse effects compared with 14% of control patients; withdrawal rates ranged from 10% with fluoxetine (6-week study) to 44% in a study with amitriptyline/atropine that lasted 15 weeks.

Chronic LBP responds to AEDs; however, literature support is scarce. Case reports have described the effectiveness of gabapentin in treating pain and functional impairment due to severe epidural fibrosis in patients with failed back syndrome (a long-lasting disabling chronic complication of lumbrosacral spine surgery). A recently published, nonrandomized, open-label, multicenter, 2-week trial also demonstrated the effectiveness of adding a transdermal lidocaine patch to the regimen of patients whose LBP was partially controlled with gabapentin. In this series, patients applied up to four lidocaine patches every 24 hours; patients reported significantly lower pain intensities, improved pain relief, and reduced pain interference with quality of life. This successful combination illustrated the benefit of combining a centrally acting adjunctive analgesic (gabapentin) with a peripherally acting drug (lidocaine). On the other hand, two studies recently reported at the American Pain Society meeting evaluated the use of pregabalin in patients with chronic LBP. Pregabalin is a structural analog of the inhibitory neurotransmitter GABA and has received an approved labeled indication from the FDA for managing neuropathic pain. In these two trials of 661 patients, end point mean pain scores for the pregabalin treatment group were not significantly different from the placebo group, although pregabalin was well tolerated.

Although literature is somewhat lacking regarding the management of chronic LBP, several therapeutic options exist. Maximizing nonpharmacological interventions and

Barlteson JD. Evidence for and against the use of opioid analgesics for chronic nonmalignant low back pain: a review. *Pain Med* 2002;3:260–71.

Salerno SM, Browning B, Jackson JL. The effect of antidepressant treatment of chronic back pain: a meta-analysis. *Arch Intern Med* 2002;162:19–24.

referring appropriate patients to psychosocial providers is important. If pharmacotherapy is required, patient- and drug-related variables must be carefully considered. It is unlikely that acetaminophen will be completely effective; however, it is widely acknowledged as a generally safe drug. Beyond that, choices include NSAIDs, opioids, or adjunctive drugs. If patients have any signs or symptoms suggestive of neuropathic pain, consider an adjunctive drug. If the adjuvant analgesic is ineffective or neuropathic pain is not likely, the practitioner must select between NSAID and opioid therapy. The long-term adverse consequences of NSAIDs are actually greater and potentially more dangerous than opioids. Careful candidate selection, close monitoring, and follow-up are critical in pain management, particularly with opioid therapy.

## Chronic Spinal Cord Injury Pain

In 1995, actor Christopher Reeve fell off a horse and severely damaged his spinal cord, leaving him paralyzed from the neck down. He died in October 2004 from a systemic infection that began from a pressure ulcer. The plight of Mr. Reeve and his advocacy for patients with SCI heightened national interest and awareness of SCI. The devastating consequences of SCI can involve every part of the body, including urinary tract and bowel problems, pressure ulcers, deep vein thrombosis and pulmonary embolus, respiratory problems, autonomic dysreflexia, weight control issues, sexual dysfunction, spasticity, and pain. Although all problems can be extremely burdensome, pain can be tremendous and severely impact quality of life.

### Pathophysiology

Spinal cord injury is defined as an insult to the spinal cord resulting in a change (either temporary or permanent) in motor, sensory, or autonomic function. The International Standards for Neurological and Functional Classification of Spinal Cord Injury has promulgated a system of describing the level and extent of injury based on neurologic function. The two primary classifications are as follows:

- Tetraplegia, previously known as quadriplegia, refers to loss of muscle strength or paralysis in all four extremities. In this case, injury to the spinal cord is in the cervical region.
- Paraplegia refers to loss of muscle strength or paralysis of the lower extremities. The degree of paralysis varies from impairment of leg movement, to complete paralysis of the legs and abdomen, up to the nipple line. Patients with paraplegia have full use of their arms and legs. Injury to the spinal cord with paraplegia is in the thoracic, lumbar or sacral areas.

Tetraplegia and paraplegia can be complete or incomplete. A complete injury means the patient is completely paralyzed below his or her lesion. An incomplete injury indicates that only part of the spinal cord is damaged, and the patient may have sensation but no movement about the lesion, or vice versa. Considering the entire SCI population, approximately one-third have incomplete

tetraplegia, about 25% have complete paraplegia, and incomplete paraplegia and complete tetraplegia are approximately 20% each.

Spinal cord injury is due to a variety of causes with almost half accounted by motor vehicle accidents. Falls and violence (such as gun or knife-related injuries) each precipitate about 20% of SCI cases, and sports-related injuries are the cause in most of the remaining cases. Up to 60 new cases of SCI occur per million population in the United States annually, with an estimated prevalence of almost 1,000 cases per million population.

The spinal cord is responsible for the body's movement and sensation and, once injured, does not repair itself. Acute pain is common after SCI and may be due to broken bones or sore joints or muscles due to the injury itself. However, in addition to a loss of sensation or motor functioning, patients with SCI commonly experience chronic pain. The incidence of SCI pain is estimated to range from 33% to 94% of affected patients, with severe disabling pain occurring in up to 37% of patients with SCI. This pain is complex in nature, likely affecting both the peripheral and central nervous system, and is frequently refractory to traditional treatment. The SCI pain encompasses musculoskeletal and visceral pain (nociceptive) and neuropathic pain, which partially explains why SCI pain is so complex to assess and treat. Neuropathic pain can be above, at, or below the level of the injury; pain occurring below the level of the injury is often rated as severe or excruciating.

### Assessment

Several classification systems have been recommended by specialists in SCI practice; however, there is no universally accepted system. The International Association for the Study of Pain commissioned a task force to address this issue. Its charge was to develop a classification system that would be sufficiently comprehensive to include most, if not all, types of pain generally associated with SCI. Table 1-10 is the proposed classification developed by this group, which has gained acceptance within the SCI literature.

Nociceptive pain includes both musculoskeletal and visceral pain. As described earlier, nociceptive pain arises from stimulation of somatic or visceral nociceptors. Musculoskeletal pain may arise from disruption of ligaments or fracture of bones causing instability. This pain is generally present at the time of injury, and rarely develops later. Pain occurs in the spinal area and may radiate toward the extremities but is not radicular in nature. The pain is exacerbated by movement, such as change in position or increased activity, and relieved by rest. This type of pain is usually responsive to nonopioids such as NSAIDs and opioids. Time to allow spontaneous healing or surgical fusion also helps relieve this pain. Muscle spasm pain is associated with both complete and incomplete SCI in some patients. It develops well after the injury and is best treated with antispasmodic drugs. Secondary overuse or pressure syndrome is due to overuse or "abnormal" use of musculoskeletal structures of the arms and shoulders. Common in paraplegics and less so in tetraplegics, this pain is commonly seen in the shoulders of those who use wheelchairs. Resting and protecting the affected areas may

**Table 1-10. Proposed Three-Tier Taxonomy for Classifying SCI Pain**

Broad Type (Tier One)	Broad System (Tier Two)	Specific Structure and Pathology (Tier Three)	Distinguishing Features
Nociceptive	Musculoskeletal	Bone, joint, muscle trauma, or inflammation Mechanical instability Muscle spasm Secondary overuse syndromes	Dull, aching, movement-related, eased by rest, opioid and NSAID responsive, located in musculoskeletal structure
	Visceral	Renal calculus, bowel dysfunction, or sphincter dysfunction	Dull, cramping, located in abdominal region with preserved innervation, includes dysreflexic headache (vascular)
Neuropathic	Above-level	Compressive mononeuropathies Complex regional pain syndromes	Sharp, shooting, burning, electric, abnormal responsiveness (hyperesthesia or hyperalgesia) Located in the region of sensory preservation
	At-level	Nerve root compression (including cauda equina) Syringomyelia Spinal cord trauma/ischemia (e.g., transitional zone) Dual-level cord and root trauma (double lesion syndrome)	Located in a segmental pattern at the level of injury
	Below-level	Spinal cord trauma/ischemia (e.g., central dysesthesia syndrome)	Located diffusely below the level of injury

NSAID = nonsteroidal anti-inflammatory drug; SCI = spinal cord injury.

Adapted with permission from IASP Press. Siddall PJ, Yezierski RP, Loeser JD. Taxonomy and epidemiology of spinal cord injury pain. In: Yezierski RP, Burchiel KJ, eds. Spinal Cord Injury Pain: Assessment, Mechanisms, Management. Progress in Pain Research and Management, Volume 23. Seattle: IASP Press, 2002:9–24.

be helpful; useful analgesics include nonopioids and opioids.

Visceral pain has a delayed onset after SCI and is identified by burning, cramping, and constant but fluctuating pain in the abdomen. This painful presentation should be assumed to be nociceptive, and the pathogenesis should be determined. If none is found and usual treatments are not successful, neuropathic pain should be considered as the origin.

As shown in Table 1-10, neuropathic pain may be above, at, or below the level of the SCI. Pain that occurs above the level of the SCI is not necessarily due to the injury, but patients with SCI may be more prone to these painful conditions due to their debility. For example, wheelchair use and transfers may increase the risk for developing peripheral nerve compression and complex regional pain syndrome. Patients with cervical SCI are at particularly high risk for developing complex regional pain syndrome in the upper limbs. This type of pain is treated with nonpharmacological interventions (e.g., exercises and application of heat) as well as drugs (e.g., NSAIDs, corticosteroids, and adjunctive analgesics such as TCAs and AEDs). Peripheral nerve compression may also be alleviated with surgical decompression.

An example of pain that originates from the level of the SCI is nerve root compression or entrapment, which results in a lancinating, burning, stabbing pain in the distribution of a single nerve root, although the pain may be bilateral. Cauda equina is a form of nerve root pain and causes burning-type pain in the legs, feet, perineum, genitals, and rectum. These painful syndromes may be deafferentation pain or due to spontaneous activity in the damaged roots of the cauda equina. Segmental deafferentation pain is neuropathic pain that occurs at the border of normal

sensation and anesthetic skin and is sometimes referred to as girdle, end zone, border zone, or transitional zone pain. The pain can be unilateral, bilateral, or circumferential and is frequently accompanied by allodynia and hyperalgesia. This type of pain usually develops within the first few months after SCI and responds best to adjunctive analgesics. Surgical interventions such as epidural or somatic root blocks, spinal cord stimulation, and other procedures may also be helpful. Syringomyelia is a disorder in which there is an obstruction to the normal flow of cerebrospinal fluid, redirecting it into the spinal cord itself, resulting in a syrinx (cyst) formation. The syrinx expands and elongates over time, destroying the center of the spinal cord. This insult should be considered with delayed onset of neuropathic pain, particularly where there is a rising level of sensory loss. Patients with this type of pain describe a constant, burning pain that may be associated with allodynia. The most effective treatment is surgical decompression of the arachnoid scar at the level of the injury to allow free flow of cerebrospinal fluid. Although the syrinx may collapse, pain may persist and is best treated with adjunctive analgesics.

Neuropathic pain below the level of the SCI is perceived more diffusely in anesthetic regions below the injury and is usually bilateral. Sometimes described as deafferentation or dysesthetic pain, or central dysesthesia syndrome, patients complain of burning, tingling, numbness, aching, and throbbing. The pain is usually constant and related to a position or activity, but it may worsen when infection is present or triggered by sudden noises or jarring movements. Below the injury pain is the most commonly experienced pain by patients with SCI (up to 40% of patients) and generally the most difficult to treat. Adjunctive analgesics are the primary therapy; intrathecal opioids and clonidine can be considered as second-line therapy.

Spinal cord injury pain is diagnosed after a thorough history and physical examination are done, and, if needed, imaging studies. Treating SCI pain is challenging, and complete pain relief is an elusive goal. Pain, rather than loss of function, is why most patients with SCI report they are unable to work. Up to 37% of patients with SCI report that if they had the chance, they would trade pain relief for loss of bladder, bowel, or sexual function. Another study evaluated how people with SCI rated their perceived difficulty in dealing with the consequences of their injury. Chronic pain was highly rated and exceeded only by the decreased ability to walk or move, loss of sexual function, and diminished ability to control bowel or bladder function.

### Management

Not surprising, although the pain rating is important, return or improvement of functional status is the overriding goal in SCI pain management. Unfortunately, achieving complete or major pain relief is a challenge in this patient population. Randomized, clinical trials of both pharmacological and nonpharmacological interventions are few, and those that exist are of small sample size and show mixed or disappointing results.

All patients with SCI will likely receive physical occupational therapy interventions and extensive patient education. Psychological counseling is also critically important, and treatment of depression as needed. Many patients with SCI pain claim benefit from using distraction as a pain-relieving technique. Other techniques include relaxation training, biofeedback, and hypnosis.

Other nonpharmacological interventions have been assessed with mixed results. Use of transcutaneous electrical nerve stimulation has had some effect for patients with muscular pain and at-level neuropathic pain, but not in patients with below-level pain. Transcutaneous electrical nerve stimulation has been shown to worsen the clinical course of acute and recent (less than 2 years post-SCI) tetraplegics, and has not been of any benefit in treating central neuropathic pain. Spinal cord stimulation has some effect in patients with incomplete lesions, painful spasms, at-level pain, or postcordotomy pain; however, efficacy tends to decline over time. Deep brain stimulation has been of limited usefulness, and has no proven long-term benefit. Experience with cordotomy, corpectomy, and myelotomy has been mixed, and adverse effects frequently outweigh therapeutic gain. Dorsal root entry zone and computer-assisted dorsal root entry zone surgical procedures destroy sensory nerves in the spinal column by “burning” them with a radio frequency or laser probe. Patients with pain in dermatomes at or just below the level of SCI, and those with unilateral pain, have had good results after Dorsal root entry zone lesions; results have been less satisfactory in patients with sacral pain or diffuse pain.

When selecting an analgesic for SCI pain, all pain complaints should be identified and thoroughly assessed. For musculoskeletal pain that is severe and acutely related to the initial trauma, opioid therapy may be the best option.

Some have advocated using tramadol as a step-down drug from opioid therapy as acute pain resolves. For chronic musculoskeletal pain, nonopioids such as acetaminophen and NSAIDs are appropriate, and opioid therapy may be required for more severe pain. As discussed above, resting the affected area allows healing (e.g., overuse syndrome). Also, SMRs may play a role in treating muscle spasms. Spasticity is defined as a motor disorder that is characterized by a velocity-dependent increase in tonic-stretch reflex, with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex. It is not always necessary to treat spasticity, but if it interferes with function, baclofen is the drug of choice. Benzodiazepines and dantrolene are alternate drugs for the treatment of spasticity.

The Agency for Healthcare Research and Quality developed guidelines titled Management of Chronic Central Neuropathic Pain Following Traumatic Spinal Cord Injury, which were published in September 2001. The guidelines acknowledge that even the definition of central neuropathic pain is unclear from the literature, but clearly encompasses neuropathic pain at-level and below-level. The guidelines reviewed 31 potentially eligible studies evaluating the pharmacotherapeutic management of SCI pain. Three studies were evaluated using opioids. One randomized, controlled, clinical trial was a double-blind, crossover design of 1-day duration evaluating intravenous infusion of alfentanil, ketamine, and placebo. Active interventions reduced continuous and evoked pain compared with placebo. Another 1-day study evaluated epidural administration of morphine or clonidine, and, if needed, epidural buprenorphine was added. Some effect was seen in most patients, but no statistical analysis was conducted. In the third study, 8 of 12 patients achieved satisfactory pain relief with an intrathecal morphine infusion.

When the Agency for Healthcare Research and Quality guidelines were published, there was one randomized, controlled trial and a case series available evaluating AEDs. The randomized, controlled trial evaluated valproate versus placebo with mixed results. The case series evaluated the efficacy of gabapentin at oral doses of 600–2700 mg/day. Investigators reported at least a 50% pain reduction in participants.

Two studies evaluated local anesthetics: mexiletine versus placebo and intrathecal lidocaine versus placebo. There was no difference in pain relief between study groups in the mexiletine trial, but a significant decrease in pain intensity and duration was noted in the lidocaine trial. Two studies performed by the same research group evaluated the effect of clonidine in SCI pain, with some beneficial effect seen. One study evaluated the effects of baclofen, trazodone, and ketamine for SCI pain. Baclofen administered intrathecally to nine patients resulted in no change in pain intensity for seven patients, and worsening of pain in the remaining two. In the trazodone study, patients received 150 mg/day orally, and no difference in pain scores was seen

compared with placebo. The 1-day ketamine trial reported some beneficial effect seen.

The Agency for Healthcare Research and Quality evidence report reviewed three studies that included drug combinations. A study of 28 patients who received electroacupuncture or a combination of carbamazepine plus amitriptyline concluded that both therapeutic modalities were safe and effective. Another study reported survey results of 145 patients receiving three different drug combinations, all of which contained amitriptyline and clonazepam plus one or two additional interventions. Reports of satisfaction with pain control were fairly low.

The Agency for Healthcare Research and Quality evidence report concluded that evidence is so limited it is impossible to draw any conclusions regarding the role of analgesics in clinical practice for patients with SCI pain. Their advice was to rely more heavily on clinical trial data assessing the use of analgesics and adjuvants in managing neuropathic pain other than SCI to best structure an analgesic regimen for patients with an SCI.

Since the publication of the Agency for Healthcare Research and Quality guidelines, several additional studies investigating the use of AEDs have been published. Lamotrigine was compared with placebo in 30 patients with SCI and at- or below-level neuropathic pain. There was no significant benefit with lamotrigine when the whole sample was evaluated; however, patients with incomplete SCI had significantly reduced pain at- or below-level injury compared with placebo. Patients with brush-evoked allodynia and wind-up-like pain in the area of maximal pain were more likely to have a positive effect with lamotrigine than patients without these evoked pains. Topiramate was reported to be effective in some case reports, warranting larger controlled studies with this drug. Oxcarbazepine was also effective in treating central pain with allodynia in a small series of patients with SCI pain.

One of the best examples of a well-designed randomized, controlled trial performed in patients with SCI pain was recently published. Researchers evaluated the use of gabapentin in 20 paraplegic patients with SCI at the thoracic and lumbar level. Pain had been present for at least 6 months and scored higher than 4 of 11 on the Neuropathic Pain Scale (representing moderate to severe pain). Patients received gabapentin or placebo over a 4-week titration period to reach the maximum tolerated dose, followed by a 4-week dosing period with maximum doses, then a 2-week washout period, followed by a crossover 4-week titration period and 4-week stable dosing period. The study was powered to detect a 3-point difference on the Neuropathic Pain Scale and a 30-point difference on the visual analog scale between placebo and gabapentin. Results showed gabapentin provided significant pain reduction for all varieties of neuropathic pain at week 4 compared with baseline, and pain scores continued to decline at week 8. Gabapentin provided more relief than placebo on all descriptors of neuropathic pain; however, neither treatment

affected Neuropathic Pain Scale scores for cold, itchy, sensitive, and dull varieties of neuropathic pain. The effective daily dose of gabapentin ranged from 1900 to 3600 mg/day. About 25% of placebo-treated patients and 65% of gabapentin-treated patients experienced an adverse effect, which resolved with dosage reduction. An additional study published recently showed that of patients with SCI pain who responded to gabapentin, more than 90% continued to respond to and tolerate gabapentin therapy 6–36 months after initiating therapy.

Clearly, additional research is needed in the area of SCI pain management, such as the gabapentin trial described above. Although the experience and evidence base is not as strong for SCI pain as it is for other neuropathic pain states (e.g., PDN or PHN), it is shameful that surveys have shown that only 44% of patients with at- or below-level pain were receiving any analgesics, and only 7% of patients were on an adjunctive drug. Working with the information currently available, as well as anecdotal experience, the following guidelines seem most reasonable. For SCI pain that is above-level (e.g., somatic musculoskeletal and visceral pain), treat pain based on experience and guidelines for patients who do not have SCI (e.g., use of nonopioids for musculoskeletal pain, with opioids and adjuvants as needed). For at-level or below-level pain, begin with monotherapy such as gabapentin. If no pain relief is achieved, try a different monotherapeutic drug with a different mechanism (see Figure 1-2). If some, but not adequate relief was achieved, add a second drug that acts by a different mechanism. If pain control is still not at goal, consider switching to or adding an additional drug, such as an NMDA receptor antagonist. If more invasively administered analgesic therapy is needed, consider intravenous or subarachnoid lidocaine; intravenous ketamine, alfentanil, or propofol; or intrathecal baclofen or morphine in combination with clonidine; these regimens all have some documented degree of effectiveness. Nonpharmacological interventions described above may be used in lieu of, or in combination with, pharmacological interventions.

As discussed previously, monitoring patient outcomes is critical. The patient's perception of pain control is highly subjective, and can be assessed only by the patient. Begin with the end in mind, determine the best and reasonable indicators of functional status, and assess achievement of those end points. Patient education is critical, particularly with a debilitating condition such as SCI. Patient's expectations for pain control must be explored and priorities established. In the words of Barry Corbet, editor of New Mobility from 1991 to 2000 and a paraplegic for 37 years, "the best noninvasive treatment for chronic pain known still, after all these years, is a combination of disattention, exercise, and a dynamite attitude." Mr. Corbet died at age 68 of bladder cancer while this manuscript was being prepared.

Yezierski RP, Burchiel KJ. Spinal Cord Injury Pain: Assessment, Mechanisms, Management. Seattle, WA: IASP Press, 2001.

Dobbs J. Chronic pain. In: Corbet B, Dobbs J, Bonin B, eds. Spinal Network: The Total Wheelchair Resource Book, 3rd ed. Horsham, PA: Nine Lives Press, 2002:90–8. Available at [http://www.newmobility.com/SN\\_pain.pdf](http://www.newmobility.com/SN_pain.pdf). Accessed September 12, 2005.

### **Table 1-11. Patient Bill of Rights in Pain Management**

#### Pain Care Bill Of Rights

As a Person With Pain, You Have the Right to:

- have your report of pain taken seriously and to be treated with dignity and respect by doctors, nurses, pharmacists, and other healthcare professionals.
- have your pain thoroughly assessed and promptly treated.
- be informed by your doctor about what may be causing your pain, possible treatments, and the benefits, risks, and costs of each.
- participate actively in decisions about how to manage your pain.
- have your pain reassessed regularly and your treatment adjusted if your pain has not been eased.
- be referred to a pain specialist if your pain persists.
- get clear and prompt answers to your questions, take time to make decisions, and refuse a particular type of treatment if you choose.

Although not always required by law, these are the rights you should expect, and if necessary demand, for your pain care.

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## **The Role of the Pharmacist in Chronic Pain Management**

Pharmacists, who are highly visible health care practitioners and frequently sought out by patients, are in an excellent position to identify patients with pain or who potentially have a pain complaint. Unfortunately, there are many barriers to good pain control, some of which originate with the patient. For example, one study published in the Journal of Pain and Symptom Management found that most Americans would rather tolerate pain than take action to relieve it. Specific findings included:

- 92% believe that pain is a fact of life;
- 82% think that it is too easy to become reliant on pain medication;
- 72% believe that a drug will not be effective with continued use; and
- 46% avoid a drug until pain becomes severe.

The American Pain Foundation has published the Patient Bill of Rights in Pain Management, shown in Table 1-11.

Pharmacists are able not only to identify patients in pain, but also to dispel myths and misconceptions about pain control. Patients may be fearful of using an opioid because of the sedation or concerns about psychological dependence. In many painful conditions, such as neuropathic pain, opioids are not first-line therapies, and adjuvant analgesics may be preferable. Knowledge of the literature and a good practice base will also enable pharmacists to make recommendations to prescribers for optimal pain management.

Of importance, pharmacists can participate in monitoring the quality of pain management. For example, analgesics are frequently implicated in medication errors, such as

mismanagement of patient-controlled analgesia therapy (see Web page of the Institute for Safe Medication Practices <http://www.ismp.org/>). As drug experts, pharmacists can have a significant impact on policy-making and political advocacy for patients in pain.

The Joint Commission on Accreditation of Healthcare Organizations has focused on appropriate pain management in the past several years. Expectations include the following:

- recognize the right of patients to appropriate assessment and management of pain;
- assess the existence and, if so, 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, and address pain assessment and management in the orientation of all new staff;
- establish policies and procedures that support the appropriate prescription or ordering of effective pain medications;
- educate patients and their families about effective pain management; and
- address patient needs for symptom management in the discharge planning process.

Pain can have a dramatic adverse effect on quality of life, and pharmacists have much to offer pain patients in terms of education, assessment and triage, selection and management of the analgesic regimen, and patient advocacy.

## **Annotated Bibliography**

1. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003;60:1524-34.

This is a mandatory reference for any practitioner who deals with pain issues. Experts in neuropathic pain convened to develop the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain. This document is a concise yet comprehensive review of the diagnosis and assessment, pathophysiology, and treatment of neuropathic pain. Evidence-based literature was used to determine first-line treatment recommendations for neuropathic pain, which include gabapentin, the 5% lidocaine patch, opioids, tramadol, and tricyclic antidepressants (TCAs). Recommendations consider clinical effectiveness, adverse effects, influence on quality of life, and cost. Thought processes for selecting a first-line agent and subsequent interventions are presented in this excellent reference.

2. Argoff CE, Katz N, Backonja M. Treatment of postherpetic neuralgia: a review of therapeutic options. *J Pain Symptom Manage* 2004; 28:396-411.

This review article, prepared by a panel of expert pain practitioners is the definitive reference on the management of post-herpetic neuralgia (PHN). The authors provide a succinct and understandable explanation of the pathogenesis of PHN and an excellent review of the literature regarding pharmacotherapeutic options to treat this painful condition.

JCAHO Expert Resources on Health Care Issues News Room. Joint Commission Focuses on Pain Management. August 3, 1999. Available at <http://www.jcaho.org/news+room/health+care+issues/jcaho+focuses+on+pain+management.htm>. Accessed September 13, 2005.

Recognizing the lack of a clear-cut treatment algorithm for the treatment of PHN, the authors provide a highly cogent discussion on designing a treatment approach. This article provides a useful summary of published literature on the treatment of PHN and serves as a valuable resource to substantiate therapeutic recommendations.

3. Rowbotham MC, Twilling L, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 2003;348:1223–32.

Rowbotham and associates conducted an excellent trial evaluating the use of an oral opioid (levorphanol) in the treatment of a variety of chronic peripheral and central neuropathic pain states. This study is useful because it clearly illustrates the benefits and risks of opioid therapy in neuropathic pain states. Practitioners frequently cite unfounded dogma that opioids have no therapeutic value in neuropathic pain; this study validates the usefulness of opioids in this role.

4. Low Back Pain or Sciatica in the Primary Care Setting. Washington, D.C.: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs National CPG Council, and Health Affairs, Department of Defense, November 1999. Office of Quality and Performance publication 10Q-CPG/LBP-99. Available at <http://www.qmo.amedd.army.mil/pguide.htm>. Accessed December 15, 2004.

The Veterans Health Administration and Department of Defense developed this comprehensive clinical practice guideline for managing low back pain (LBP) or sciatica in the primary care setting. A flow chart is included and explained in detail for screening patients with LBP, then treating acute and chronic LBP. Accompanying text provides both an annotated and expanded discussion. Tables and appendices provide quick reference information and a variety of clinical tools that are useful in caring for LBP patients. An extensive bibliography is included. This evidence-based, well-referenced resource is mandatory for practitioners who provide care for consultation on patients with LBP.

5. Levendoglu F, Ogun CO, Ozerbil O, et al. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. *Spine* 2004;29:743–51.

Given that the literature on spinal cord injury (SCI) pain is so scarce, this landmark trial is welcome. This prospective, randomized, double-blind, crossover trial demonstrated the efficacy, effective dose, and adverse effect profile of gabapentin compared with placebo in patients with moderate to severe SCI neuropathic pain, including dysesthetic pain. The investigators used sound research strategies and evaluated several aspects of pain control, including pain intensity (Neuropathic Pain Scale and Visual Analogue Scale) and an adapted Lattinen test to assess subjective intensity and frequency of disability due to pain and quality of sleep. This is a solid piece of evidence that can be used to substantiate the use of gabapentin in chronic SCI pain.