Treating Chronic Pain: New Knowledge, More Choices

By Christine E Whitten, MD
Marilee Donovan, RN, PhD
Kristene Cristobal, MS

Introduction

In routine medical practice, treatment for primary pain fails to achieve adequate relief in at least 40% of patients even though effective treatments are currently available.[1] Many clinicians were trained years ago, when little was known about pain. The rapid expansion of knowledge about pain mechanisms challenges health care practitioners to keep their knowledge base current. Myths, misconceptions, and the resulting fears often bridge gaps in this knowledge. Lack of knowledge limits treatment choices and may hinder desired patient outcomes by allowing pain hypersensitivity and progressive dysfunction to develop (Table 1).

This article—the third in a series about management of chronic pain—offers practical treatment advice based on the newest science. Readers who seek more detail are referred to several recent reviews that provide more complete descriptions of cellular mechanisms.[2,3]

Multimodal Treatment: Importance for Managing Pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional response associated with actual or potential tissue damage or described in terms of such damage."[4] Perception of pain is a dynamic interaction between sensory, emotional, and behavioral factors (Table 2). Figure 1 describes normal pain processing and the pathologic changes that accompany development of chronic pain. Pain processing includes six major components: transduction, inflammation, conduction, transmission, modulation, and perception.

Transduction

Acute pain processing (nociception) begins when imminent or real injury from a thermal, chemical, or mechanical source stimulates peripheral endings of sensory neurons (nociceptors). Nociceptors translate (transduce) the physical stimulus into an electrical signal which, if strong enough, triggers an action potential. The effect is analogous to lighting a fuse: Not every stimulus is strong enough to "light the fuse;" but, once "lit," the signal progresses along the length of its course unless the signal is interrupted.

Local Inflammation

Trauma also triggers damaged cells to release inflammatory substances that increase sensitivity to pain: The resulting flood of prostaglandins, substance P,

The rapid expansion of knowledge about pain mechanisms challenges health care practitioners to keep their knowledge base current.

Table 1. Consequences of clinicians lacking current knowledge of pain management

Practice Issue	Potential Problems
Failure to use multimodal approach	• Miss the benefits of physical, behavioral, and psychological approaches to help retrain the central nervous system and maximize functional recovery.
Failure to target the mechanism of pain generation (somatic, inflammatory, neuropathic)	• Suboptimal pain management • Avoidable costs when treatment ineffective
Failure to treat neuropathic pain with adjuvant medications (eg, antidepressants, anticonvulsants)	• Worsening nervous system hypersensitivity • Suboptimal pain management
Heavy reliance on short-acting opioids instead of prescribing long-acting opioids	• Increased breakthrough pain, disturbed sleep • Development of opioid tolerance • Acetaminophen toxicity (combination drugs) • Increased risk of addiction in sub-population with potential for substance abuse

Christine E Whitten, MD, (not pictured) is an SCPMG anesthesiologist in San Diego, CA. She is the Southern California Coordinator of Pain Management and the Clinical Lead for the CMI Chronic Pain Condition Group. E-mail: christine.e.whitten@kp.org.
Marilee Donovan, RN, PhD, (left) is a Manager in the Regional Pain Clinic in Portland, OR. E-mail: marilee.i.donovan@kp.org.
Kristene Cristobal, MS, (right) is the Care Management Institute's National Project Manager for Chronic Pain and the Project Manager for Culturally Competent Care. E-mail: kristene.cristobal@kp.org.

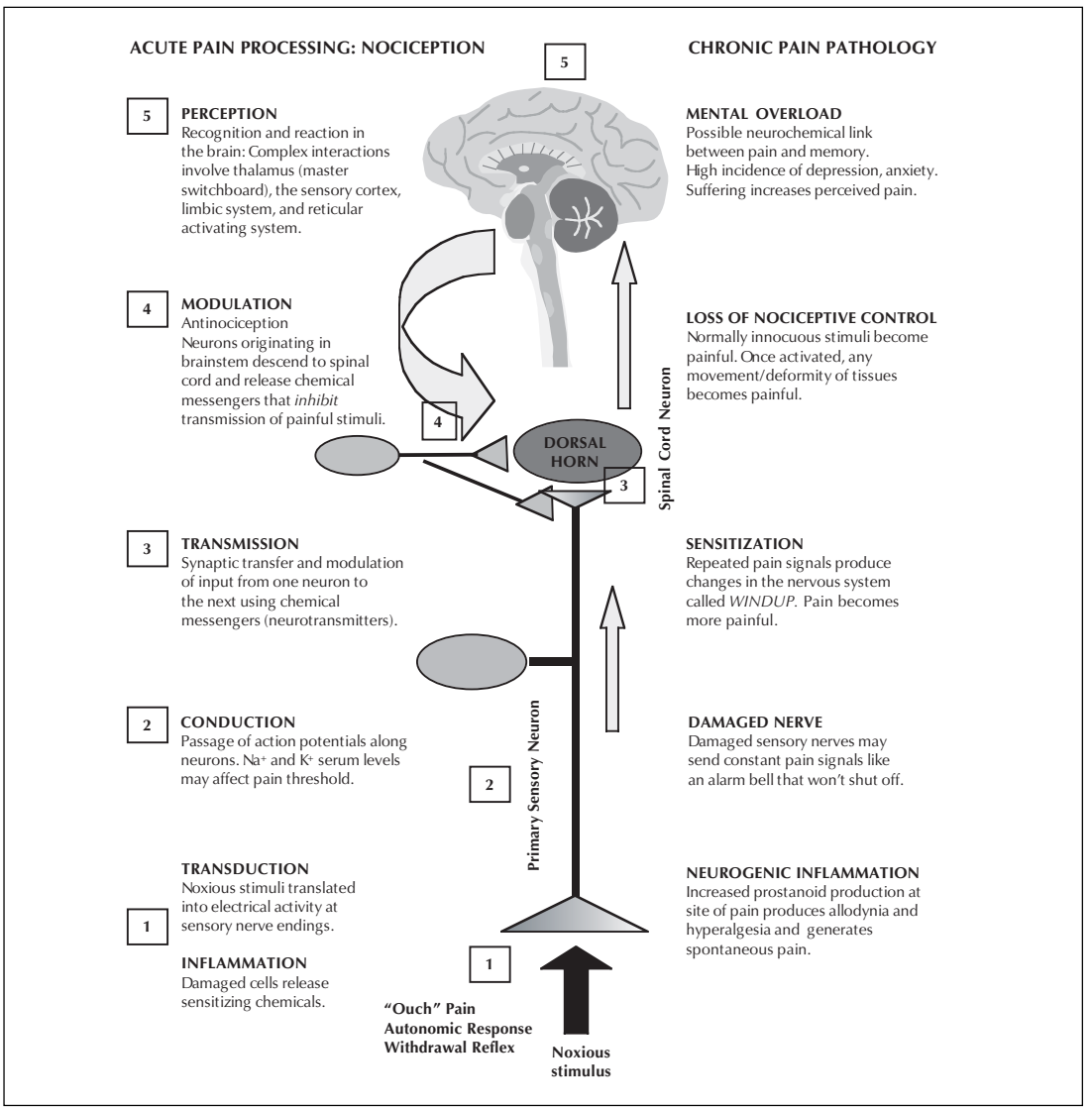


Figure 1. Diagram compares acute and chronic pain processes and pathways.

Patients with chronic pain have *reduced* pain thresholds and therefore feel pain more intensely.

bradykinin, serotonin, and histamine causes the area of injury to become red, swollen, and painful and leads to *hyperalgesia*, a lowered pain threshold. Increased numbers of action potentials and spontaneous discharges occur in response to stimuli. Not only do painful stimuli become more painful than usual, but previously nonpainful stimuli can become quite painful (allodynia). Increased skin sensitivity from sunburn is a good example of both allodynia and hyperalgesia.

Conduction

The pain signals are then *conducted* along nerve fibers via the passage of action potentials along neurons. Sodium ions enter during depolarization, then potassium ions leave to restore baseline negative charge. The type of fiber carrying the signal affects the quality of the pain. A-delta fibers carry sharp, well-localized pain, whereas C fibers carry poorly localized burn and ache from around the area of injury. However, because they are nonmyelinated, C fibers are more easily damaged. In shingles and in painful diabetic neuropathy, C fibers bear the brunt of injury. Not surprisingly, the quality of pain in these conditions is often a burning allodynia.

Transmission

Wherever one nerve conduction pathway ends and another begins, neurotransmitters—including glutamate, substance P, norepinephrine, dopamine, and serotonin—

transmit the signal across the synaptic gap separating them. Transmission occurs at three junctions: first, between nociceptor and dorsal horn of the spinal cord; second, between the spinal cord and the thalamus and brainstem; and third, from the thalamus into the cerebral cortex. Figure 2 compares sensitive and nonsensitive patient responses to pain as shown in MRI scans.[5] Data on individual differences were published in Coghill RC, et al.[6]

Modulation

Modulation—adjustment of pain intensity—is performed by an extensive antinociceptive (antipain) system. Opioid medications work because opioid receptors already exist to bind endogenous opioid substances, such as endorphins and enkephalins. The pain of acute injury often fades within minutes. The injury has not yet healed, but the antinociceptive system reduces pain intensity, allowing return to function.

One way to conceptualize this pain inhibition is the Gate Theory, first introduced by Melzack and Wall.[7] Nerves are analogous to telephone cables: Both carry many types of calls or signals, but the total number of these carried at any moment is limited. Checks and balances built into the system help triage those signals. For example, if you hit your thumb with a hammer, rubbing the injury decreases pain because rubbing generates inhibitory signals that "close the gate" to the pain.

An intense level of pain for a short time produces stress-analgesia, a short-term protective mechanism whereby the limbic system inhibits pain signals within the spinal cord. (On the battlefield, for example, a soldier may not feel a wound until after fighting stops.) However, the spinal cord is excited by prolonged stimulation of the limbic system by either stress or pain, and this prolonged stimulation can produce hypersensitivity to pain. Patients with chronic pain have *reduced* pain thresholds and therefore feel pain more intensely.

Pain is diminished by factors which "close the gate" and is intensified by factors that "open the gate." Medications, emotions, behaviors, and thoughts both open and close the gate by affecting transmission and modulation.

Perception of Pain

When pain signals ultimately enter the brain through the thalamus—the brain's "master switchboard"—these signals are then routed to regions of the brain involved with sensation, autonomic nervous system, motor response, emotion, stress, and behavior. The complex interactions of all these areas define the patient's perception of pain.

Research shows that patients who describe themselves as more sensitive to pain actually have a heightened response (shown on functional MRI scans) in the three areas of the brain responsible for pain perception: the thalamus, limbic system, and periaqueductal gray area.[8] Distraction—long known to help some patients decrease the level of pain—decreases pain-related brain activity as seen on functional MRI scans.[9] A distracted person literally processes less pain. When focusing on pain, a

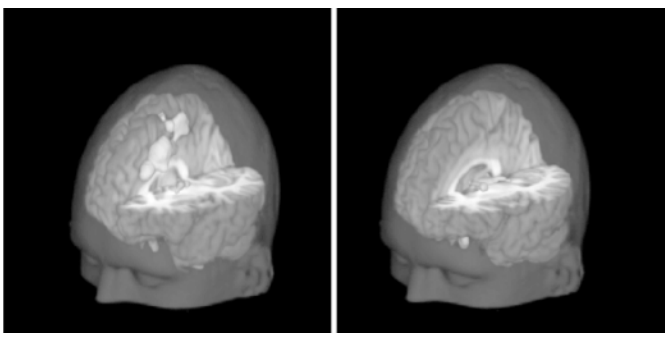


Figure 2. Functional MRI scans show brain response in pain-sensitive (left) and nonsensitive (right) patients. *(Reproduced by permission of the author from: Coghill RC. Brain mechanisms of pain: Overview. Section on: Neural correlates of inter-individual differences in the subjective experience of pain [homepage on the Internet]. [cited 2005 Oct 4] Available from: http://www1.wfubmc.edu/Nba/Faculty/Labs/coghill/Individual+Differences.htm.[5])*

Table 2: Factors influencing pain

Factors that CLOSE the gate decrease pain	Factors that OPEN the gate increase pain
Physical • Comfortable furniture that fits (beds, chairs, car seats) • Heat/cold • Pacing activities • Adequate rest • Massage	**Physical** • Inactivity/deconditioning • Poor or nonrestorative sleep
Chemical • Medications • Diet: eg, Mg^{++}, Ca^{+}, vitamin B complex	**Chemical** • Drug and alcohol dependence • Nicotine
Behavioral • Relaxation • Direct, rewarding communication • Humor • Pleasurable activities • Relaxation/meditation/prayer	**Behavioral** • Trying to do too much too quickly • Difficult relationships • Social isolation • Stress • Persistent worry
Thoughts and emotions • Optimism/positive outlook • Setting realistic goals • Affirming of self	**Thoughts and emotions** • Negative outlook/catastrophizing • Hopelessness/worry • Suppressing emotions • Anger • Depression/anxiety • Focusing on pain
Structural • Surgery (sometimes)	**Structural** • Surgery (sometimes) • Trauma (eg, broken bones, inflammation, extensive dental work)

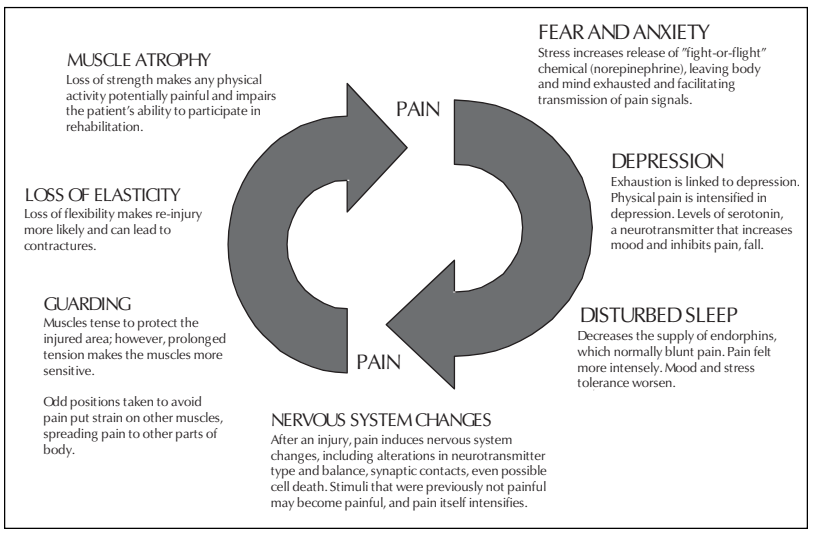


Figure 3. Diagram shows "vicious cycle" of pain.

person feels more pain, and those areas of the brain "light up." It's not surprising that many patients with chronic pain have more pain at night, when surroundings are quiet and have fewer stimuli to compete with the pain.

Fear, anxiety, depression, disturbed sleep, and central nervous system changes lead to other physical impairments in a "vicious cycle," which, if left unbroken, can worsen pain (Figure 3). Multimodal treatment is therefore vital to pain care (Table 3). Helping patients learn to better manage the pain inhibits pain transmission and improves pain management.[10] Exercise and psychological treatment are effective for treating chronic pain because these treatments may help retrain the nervous system to reestablish more normal neural connections.[11] Especially important is for clinicians to recognize and treat depression and anxiety, which affect 20% to 50% of patients with chronic pain.[12] These conditions affect patients' ability to participate in their own self care and recovery as well as altering the balance of neurotransmitters involved in modulating pain.

Table 3. Multimodal approach to treating chronic pain

Blocking the pain mechanism	Potential multimodal treatments
Prevent peripheral nociception	• Prevent pain; treat early and aggressively • Start low and go slow • Pacing; positioning • Ice • Membrane stabilizers: eg, gabapentin • Mg^{++}, Ca^{++}, vitamin B complex • NSAIDs • Block COX-2 induction in inflammation
Prevent gene transcriptional changes	• TCA, opiates, Ca/Na channel blockers, anticonvulsants • Inhibit COX-2 induction • NMDA antagonists: • methadone, dextromethorphan, ketamine
Membrane stabilizers/decrease membrane excitability	• Local anesthetics • Ca/Na channel blockers, anticonvulsants • TENS/DCS; acupuncture
Increase neuromodulation at multiple sites	• Acupuncture, manual therapies • TENS, DCS • Hypnosis; Distraction • Education, reduction of anxiety/depression • Opiates; TCAs • Have fun • Placebo
Disrupt transmission of peripheral impulse to cord, thalamus, and cortex	• Ablation: Neurolytic, radiofrequency, cryoablation, neurosurgery • Implantable devices

Pathologic Mechanisms of Chronic Pain

AMPA and NMDA receptors are important to our understanding of how acute pain becomes chronic pain.

In acute pain, glutamate (an important neurotransmitter that acts on many different types of pain-related receptors) attaches to the AMPA receptors, which are present on the sodium and potassium channels of the dorsal horn neurons. If enough neurotransmitter effect occurs, another action potential is generated. The pain signal is propagated along the second leg of its journey toward the thalamus and then from the thalamus to the cortex.

In contrast, NMDA receptors at the cleft between one neuron and the next are apparently strongly involved with development of chronic pain. Prolonged stimulation of an AMPA receptor changes the resting polarization state of the membrane and, as a result, the magnesium ions that plug the neighboring NMDA receptors are removed. This process primes the NMDA receptors for glutamate activation, thus triggering a cascade of events leading to central nervous system hypersensitization ("central windup").[13,14] Activation of NMDA alters the balance of neurotransmitters; induces synthesis of gene proteins; triggers changes in receptor binding and the firing threshold of nerves; promotes creation of new synaptic contacts; and can even result in cell death. NMDA activation and central windup have several important implications for chronic pain:

- Threshold receptivity of surrounding nerves is lowered, thereby producing hyperalgesia.
- Nonpain nerves begin to fire and carry pain messages, thereby causing allodynia.
- The threshold of opioid mu receptors is increased, thereby causing
  - Decrease in effectiveness of endogenous and exogenous opioids
  - Greater need for antinociceptive input, which

is necessary for stopping pain conduction
- Tolerance to opioid substances.

- Threshold sensitivity to catecholamines is lowered, thereby facilitating transmission of pain signals.
- Pain fields spread to adjacent neurons in the spinal cord and nondermatomal representation results. At first, uninjured areas of the body close to the injury begin to hurt; then as additional nerves are recruited, areas increasingly further away become affected.
- All pain is felt as more severe.

In the short term, these changes allow healing by forcing protection of the injured area. "Windup" usually resolves as the injury heals; in some patients, however, these changes persist. The more severe the pain and the longer it persists, the more likely that the change will become permanent.[3] We do not yet know the exact combination of pain severity, duration, etiology, and genetic predisposition that leads to chronic pain, but one important conclusion is clear: Inadequate pain control increases the likelihood that pain will become chronic.

Neurogenic inflammation is an additional mechanism that produces peripheral nervous system sensitization to pain. Increased prostanoid production at the injury site may cause widespread induction of COX-2 as well as activation of macrophage-like cells within the spinal cord. These cells release cytokines and chemokines, which act on neurons and glia to alter gene transcription. This alteration produces allodynia and hyperalgesia, which manifest as spontaneous pain.

Pain that is poorly controlled or prolonged can also inhibit the antinociceptive system. Fibromyalgia, a condition that has been erroneously considered factitious, is now thought to be a debilitating disease caused by antinociceptive dysfunction. In fibromylagia patients, positron-emission tomography (PET) and functional MRI scans show changes in pain processing.[8,14]

Pain Management: Target the Type of Pain When Possible

Given that painful medical conditions may be inflammatory or neuropathic (Figure 4), the type (cause) of a patient's pain should be a factor dictating treatment choice. Long-term use of opioid drugs is not the best approach for treating all pain syndromes. Pain from inflammation responds better to antiinflammatory drugs. Widespread central induction of COX-2 contributes to generalized aching, loss of appetite, and changes in mood and sleep cycles that often accompany any illness with an inflammatory component.[2] Thus, nonsteroidal antiinflammatory drugs (NSAIDs) and COX-2 inhibitors have high utility in many common pain states. However, patients receiving long-term therapy with these drugs are put at potential risk of complications (eg, gastrointestinal bleeding) by the ubiquity of COX receptors in multiple organ systems. Several COX-2 inhibitors were recently withdrawn from the market because of concerns about possible cardiovascular complications.[15] These drugs offer little to no benefit to patients whose pain results from abnormal excitability of sodium channels, as in painful diabetic neuropathy.

Neuropathic pain—pain caused by nervous system pathology, such as peripheral nerve injury or spinal cord injury—often responds better to adjuvant medication, such as anticonvulsant or antidepressant drugs. Without restoring nerve function, adjuvant medication can reduce the burning quality of pain in many patients by directly affecting function of sodium channels as well as other mechanisms of nerve transmission and conduction. By limiting excitation and enhancing inhibition, these classes of drugs can modulate hypersensitivity-related changes of the nervous system.

Opioid drugs effectively treat nociceptive pain that has no coexisting nervous system pathology. In general, however, opioid drugs are much less effective for treating neuropathic pain, because windup decreases opioid efficacy by a variety of mechanisms, including decreasing the number of mu receptors.[2] This generalization does not apply to all patients; in some patients, neuropathic pain does respond to opioids, although the effective dose may be higher than expected.[16]

Many patients have coexisting nociceptive and neuropathic pain that may require a combination of medi-

… the type (cause) of a patient's pain should be a factor dictating treatment choice.

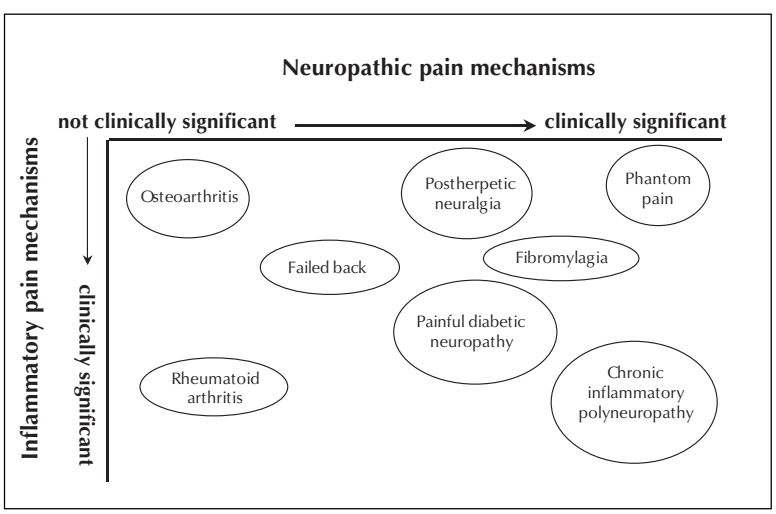
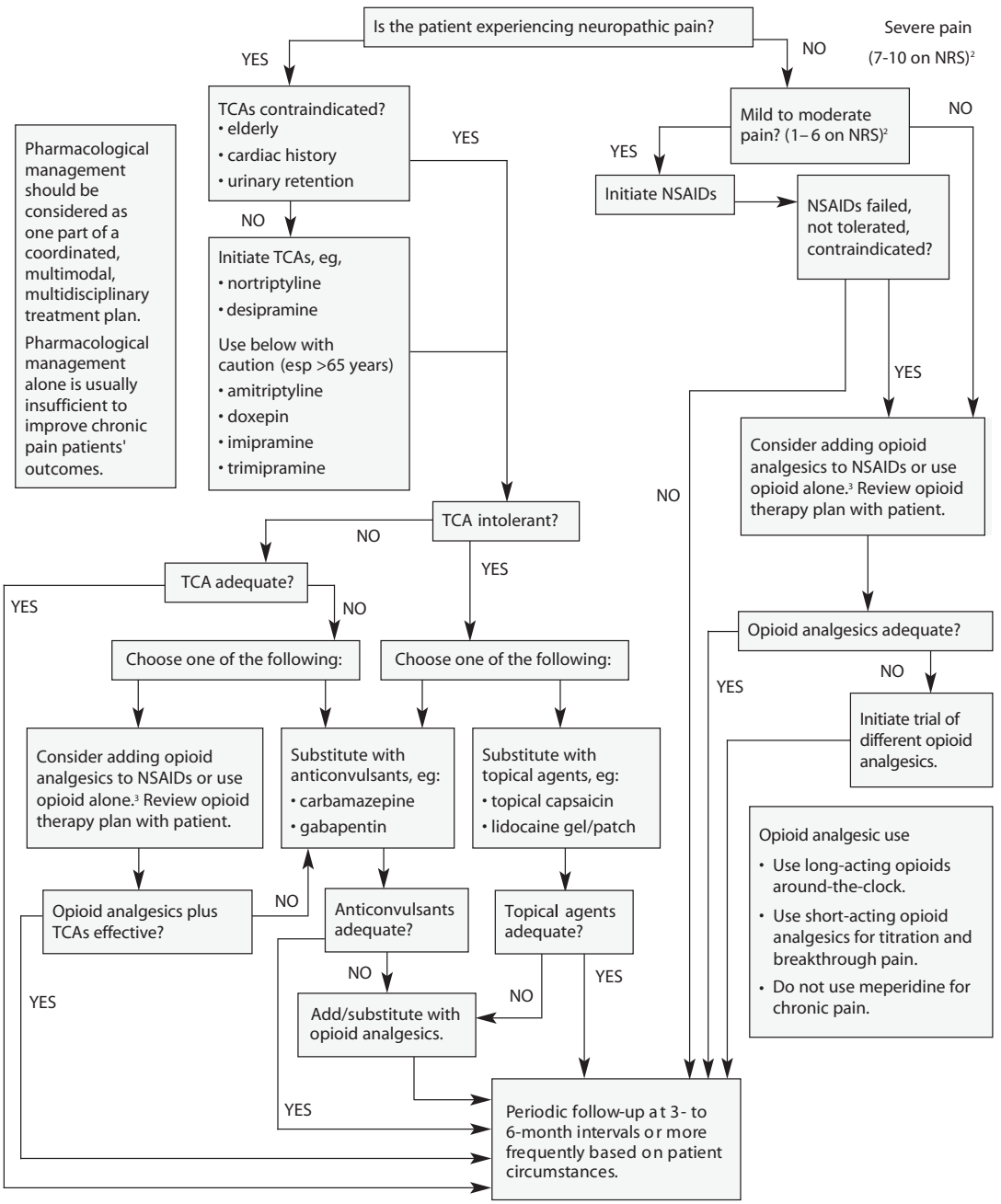


Figure 4. In chronic pain syndromes, pain is often generated by more than the mechanism at the receptor level. To optimize therapy, treatment must be matched to the pain mechanism.

Pharmacological Management of Chronic Pain[1]



[1] If acute pain patient is at high risk for developing chronic pain, treat aggressively using similar algorithm.
[2] More significant functional impairment (eg, 7-10 on functional impairment scale) may indicate more aggressive treatment.

Note: Use antiarrhythmics only with referral to pain medicine specialist.
Invasive pain management interventions, eg, therapeutic nerve blocks, are not addressed by these guidelines.
Please confer with your pain management specialist.

Figure 5. Flowchart shows recommended pharmacological management of chronic pain. *(Reproduced with permission of the publisher from: Kaiser Permanente. Care Management Institute. Guide to chronic pain assessment and management in primary care [monograph on the Intranet]. [Oakland (CA): Care Management Institute]; 2004. [cited 2005 Mar 4] Available from: cl/kp.org/pkc/national/cmi/programs/chronicpain/files/clintools/CPtrifold04.pdf.[18])*

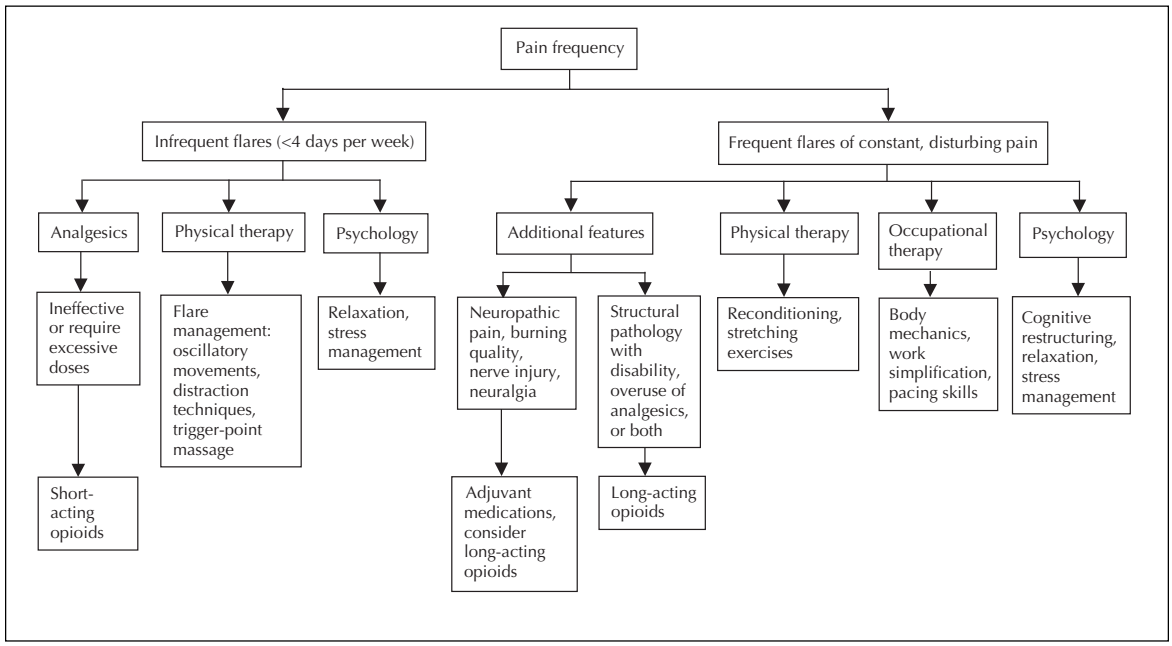


Figure 6. Algorithm for multimodal management of chronic pain. *(Adapted and reproduced with permission of author and publisher from: Marcus DA. Treatment of nonmalignant chronic pain. Am Fam Physician 2000 Mar 1;61(5):1331-8, 1345-6.[11])*

cations, including opioid drugs. For instance, opioid agents are often effective for treating postherpetic neuralgia. Although most patients with fibromyalgia do not need opioid drugs, some affected patients have pain that is so severe and disabling that opioid drugs are necessary for improved function. In a typical primary care practice of 2500 patients, approximately 1% of these members have severe disabling pain with fibromyalgia as one of the interacting causes.[17] If even 5% of these patients need opioid drugs to improve function, then every primary care practitioner has one or two patients with fibromyalgia who may benefit from opioid therapy. The patient's medical history, description of pain quality, and clinical responses should guide multimodal treatment choices (Figures 5[18] and 6[11]).

When to Suspect Neuropathic Pain and Nervous System Hypersensitivity

Suspect neuropathic pain when the pain is described as burning, shooting, lancinating, "pins and needles," or a strange sensation (eg, crawling insects). Many patients with neuropathic pain have allodynia. In patients with neuropathic pain, physical examination may show no obvious cause of the pain. Examples include *painful* diabetic neuropathy, postherpetic neuralgia, and complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy (RSD).

Early CRPS is often considered one of the few conditions warranting urgent consultation with a Pain Medicine Specialist. Signs of possible CRPS in an extremity include:

- Allodynia and/or hyperesthesia seen at physical examination
- Abnormal skin color (often ruddy or bluish)
- Temperature 1°C higher or lower in the affected extremity than in the opposite limb
- Edema
- Pseudomotor activity (increased sweating or dry skin).

Firstline treatment for neuropathic pain is secondary amine tricyclic antidepressants (eg, nortriptyline, desipramine).[19] In adults older than 65 years, tertiary amines (eg, amitriptyline, doxepin) should be used with caution because of their strong sedative, anticholinergic, and orthostatic hypotensive effects in this population. Caution and increased monitoring are recommended when using tricyclic antidepressants in patients who have severe heart disease, symptomatic prostatic hypertrophy, neurogenic bladder, dementia, or narrow-angle glaucoma.[19]

Firstline treatment for neuropathic pain is secondary amine tricyclic antidepressants (eg, nortriptyline, desipramine).[19]

Some patients with chronic pain achieve effective analgesia by using considerably lower doses of antidepressants than necessary to treat depression; in nearly half of this population, however, an antidepressant dose may be necessary to achieve pain relief. Benefit may be seen within two weeks or may be delayed for several weeks. Starting at a low dose and slowly increasing the dose by

titration is important to minimize side effects, which hinder compliance with a regimen that needs time to become effective.

For patients who do not respond to or tolerate tricyclic antidepressant agents, recommended alternatives include:

- Adding an opioid analgesic to current tricyclic antidepressant therapy
- Starting anticonvulsant therapy, eg, with carbamazepine (for trigeminal neuralgia), phenytoin, or gabapentin.

Although no more effective than tricyclic antidepressant agents or other anticonvulsant drugs, treatment with gabapentin (Neurontin) is an option for older adults and for patients taking medication for comorbid conditions.[20] Although gabapentin too can cause sedation and confusion, this drug may be safer in this group of patients because it has fewer drug-drug interactions.[20] The high cost of gabapentin, however, can be a hardship both to patients and to practitioners.

When suspected neuropathic pain is not responding, early referral to a Pain Medicine Specialist is recommended. The longer pain remains severe, the worse it can become and the more resistant to treatment.

Doses of long-acting opioid drugs should be given at fixed intervals and not on an as-needed basis.

Long-Acting Opioid Drugs May be Preferable for Some Patients with Chronic Pain

Opioid drugs—the class of drugs with the longest history of use for pain management—are also the drugs most often avoided because of fears of side effects, social stigma, and potential regulatory oversight. The recognition that chronic pain is associated with measurable pathologic change has helped to prompt a shift in philosophy toward considering opioid treatment for chronic, nonmalignant pain. However, a key criterion should be to consider use of these drugs only if they improve patient function. The patient must take an active role in self-management, including following recommendations for activity, exercise, lifestyle, and use of medication.

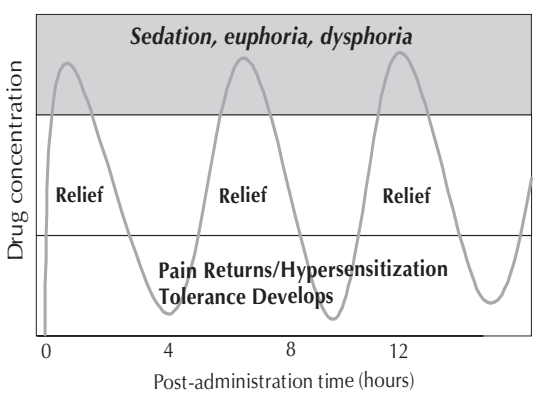


Figure 7. Graph shows disadvantages of using short-acting opioid drugs to treat chronic pain.

Long-term use of opioid drugs is not innocuous. Indeed, administration of high-dose opioid drugs can, in rare cases, produce nervous system hypersensitivity itself, probably through the activation of the NMDA receptor.[21] Theoretically, this hypersenitization would be more likely with use of short-acting opioid agents because of the frequent rise and fall of serum levels.

Key organizations that strongly support use of opioid drugs to treat chronic pain have published consensus statements to guide prescription of these drugs.[22,23] These statements emphasize the importance of a standardized approach in which the drug regimen is initiated only after the physician has assessed the relative risks and benefits of long-term opioid therapy. Long-term opioid therapy should be considered only when

- Nonopioid drug treatment and nonpharmacologic management is inadequate; and
- The pain substantially impairs the patient's quality of life and activities of daily living.

Short-acting opioid drugs are extremely useful for short-duration pain or flares. Many patients who have mild chronic pain are very satisfied with use of short-acting agents (eg, 2-4 tablets a day). These agents can also have a limited role in treating "breakthrough pain" in patients with more severe chronic pain.

The problem with short-acting opioid drugs for management of moderate to severe chronic pain is that their rapid rise and fall in blood levels creates short-lived analgesia (Figure 7). This situation:

- Puts patients at risk for acetaminophen toxicity from taking a combination product containing acetaminophen
- Facilitates development of opioid tolerance, which increases the likelihood of escalating medication needs
- Can disrupt sleep (when analgesia is lost)
- Makes patients focus on their medication instead of on their function or progress
- Provides palpable euphoria at peak levels, raising risk of activating addiction in patient prone to substance abuse.

General consensus maintains that use of long-acting opioid drugs should be considered when chronic pain is no longer well managed by short-acting opioid drugs (ie, usually when use reaches 6-8/day on a regular basis). Doses of long-acting opioid drugs should be given at fixed intervals and not on an as-needed basis.

Unfortunately, patients and some clinicians may erroneously fear that the use of long-acting opioid drugs—especially methadone—may either lead to or be interpreted as evidence of drug addiction. Long-acting opioid drugs have some key advantages (Figure 8):[24]

- Use of these drugs attenuates the rise and fall of drug levels in the blood and correlates with smoother overall pain control.
- Miniwithdrawals and minirebounds do not occur as they sometimes do with short-acting opioid drugs.
- Theoretically, drug tolerance should evolve more slowly than with short-acting opioid drugs.
- Long-acting opioid drugs are not compounded with acetaminophen; the risk of liver and renal toxicity is thus avoided.
- Dosing is more convenient, and compliance may therefore improve.
- By improving pain control and by lengthening the duration of relief, sleep is improved to allow 6-8 (or more) uninterrupted hours of sleep.
- Long-acting opioid drugs should be less likely to trigger addictive behavior and generally have lower potential for drug diversion.

Clinically significant genetic variation exists in mu receptors and possibly in other opioid receptors.[25,26] Therefore, failure of one opioid analgesic agent cannot predict patient response to another opioid agent. If the initial opioid analgesic agent is ineffective in controlling pain or if side effects are unacceptable, a different opioid drug should be prescribed.

Opioid drugs are classified into six general families: 1) codeine and morphine; 2) oxycodone, oxycodone/APAP products, and long-acting oxycodone; 3) hydrocodone/APAP products, which are related to hydromorphone (Dilaudid); 4) fentanyl; 5) methadone; and 6) meperidine, which should never be used for chronic pain or for any pain requiring more than a single dose.[27] When switching from one opioid family to another, or to a different route of administration, decrease the equianalgesic dose by 30% due to incomplete cross-tolerance. Then, titrate up to clinical response.

Methadone is increasingly used in pain management programs. This drug provides good analgesia with minimal euphoria. Methadone also is an NMDA inhibitor; therefore, its use may help to rebalance nervous system input. However, methadone has unpredictable pharmacokinetics and accumulates with repeated dosing, often requiring a decrease in dose size and frequency. Consultation with a pain medicine expert is highly recommended when initiating treatment with methadone.[24] After the patient's pain has stabilized, however, methadone analgesia can be managed in a primary care environment.

Recalcitrant Pain

Reassess your patients periodically for adequate pain control and side effects. Patients often do not take any medication consistently and correctly over time. As the cost of medications becomes a more critical factor for our members, we have noticed a cost-based trend toward not filling prescriptions. If pain is continuing, check to see whether patients are taking their medications correctly and are following the care plan. Pain that persists despite optimal medical management should be referred to your Pain Medicine Program for consultation and for recommendations. Moderate- to high-risk patients who do not respond to aggressive treatment should be referred early to try to minimize development of central hypersensitization.

Creative, mechanism-specific, multimodal treatment can help your patients with chronic pain to regain their lives. Pain reduction and maximized function should be the treatment goals. Active participation of the patient in his or her own self care is vital for improving pain management. Care plans must address reconditioning as well as improving function, sleep, and mood as well as reducing nociception and enhancing neuromodulation. For more discussion of these topics, see the first two articles in this series, ie, *Pain Management Doesn't Have to be a Pain*[28] and *Chronic Pain is a Chronic Condition, Not Just a Symptom*.[29] Additional information regarding these and other issues related to chronic pain can be found in the CMI Chronic Pain Guidelines at: http://cl.kp.org/pkc/national/cmi/programs/chronicpain/management.html.

Creative, mechanism-specific, multimodal treatment can help your patients with chronic pain …

In the words of Albert Schweitzer: "We must all die. But that I can save him from days of torture, that is what I feel

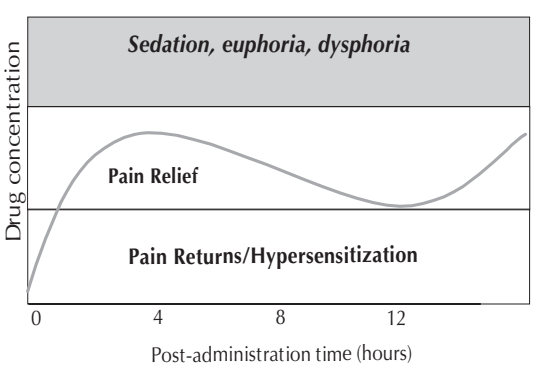


Figure 8. Graph illustrates how long-acting opioid drugs provide smoother pain control than do short-acting opioid drugs for treating chronic pain.

as my great and ever new privilege. Pain is a more terrible lord of mankind than even death himself."[30:62] ❖

References

1. Glajchen M. Chronic pain: treatment barriers and strategies for clinical practice. J Am Board Fam Pract 2001 May-Jun:14(3):211-8.
2. Woolf CJ; American College of Physicians; American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004 Mar 16:140(6):441-51.
3. Brookoff D. Chronic pain: 1. A new disease? Hosp Pract (Off Ed) 2000 Jul 15;35(7):45-52, 59.
4. International Association for the Study of Pain. IASP Pain Terminology [homepage on the Internet; about 8 screens]. [cited 2005 July 19]. Available from: www.iasp-pain.org/terms-p.html.
5. Coghill RC. Brain mechanisms of pain: Overview. Section on: Neural correlates of inter-individual differences in the subjective experience of pain [homepage on the Internet]. [cited 2005 Oct4]. Available from: www1.wfubmc.edu/Nba/Faculty/Labs/coghill/Individual+Differences.htm.
6. Coghill RC, McHaffie JG, Yen YF. Neural correlates of interindividual differences in the subjective experience of pain. Proc Natl Acad Sci USA 2003 Jul 8;100(14):8538-42. Epub 2003 Jun 24.
7. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965 Nov 19;150(3699):971-9.
8. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum 2002 May;46(5):1333-43.
9. Frankenstein UN, Richter W, McIntyre MC, Remy F. Distraction modulates anterior cingulate gyrus activations during the cold pressor test. Neuroimage 2001 Oct;14(4):827-36.
10. Galer G, Dworkin R. A clinical guide to neuropathic pain. New York: McGraw-Hill; 2000. p 30-3.
11. Marcus DA. Treatment of nonmalignant chronic pain. Am Fam Physician 2000 Mar 1;61(5):1331-8,1345-6.
12. Banks SM, Kerns RD. Explaining high rates of depression in chronic pain: a diathesis-stress framework. Psychol Bull 1996 Jan;119(1):95-110.
13. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003 Nov;60(11):1524-34.
14. Staud R, Smitherman ML. Peripheral and central sensitization in fibromyalgia: pathogenetic role. Curr Pain Headache Rep 2002 Aug;6(4):259-66.
15. Drazen JM. COX-2 inhibitors—a lesson in unexpected problems. N Engl J Med 2005 Mar 17;352(11):1131-2. Epub 2005 Feb 15.
16. Irving GA, Wallace MS. Pain management for the practicing physician. New York: Churchill Livingstone; 1997.
17. Kaiser Permanente. Care Management Institute. Kaiser Permanente chronic pain outcomes report: annual report: data from 2001 and 2002 [monograph on the Intranet]. [Oakland (CA)]: Care Management Institute; 2003 [cited July 20, 2005]. Available from: http://cl.kp.org/pkc/national/cmi/dept/measurement/reports/cp_I/toc.html.
18. Kaiser Permanente. Care Management Institute. Guide to chronic pain assessment and management in primary care [monograph on the Intranet]. [Oakland (CA): Care Management Institute]; 2004. [cited 2005 Mar 4] Available from: http://cl.kp.org/pkc/national/cmi/programs/chronicpain/management.html (click on "National Guidelines"; click on "10. Chronic Pain").
19. Portenoy RK, McCaffery M. Adjuvant analgesics. In: McCaffery M, Pasero C, editors. Pain: clinical manual. 2nd ed. St Louis, (MO): Mosby; 1999. p 300-61.
20. Beydoun A. Postherpetic neuralgia: role of gabapentin and other treatment modalities. Epilepsia 1999;40 Suppl 6:S51-6; discussion S73-4.
21. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med 2003 Nov 13;349(20):1943-53.
22. American Academy of Pain Medicine, American Pain Society. The use of opioids for the treatment of chronic pain: a consensus statement from the American Academy of Pain Medicine and the American Pain Society [monograph on the Internet]. Glenview (IL): American Academy of Pain Medicine and American Pain Society; 1997 [cited 2005 Aug 10]. Available from: www.ama-assn.org/ama1/pub/upload/mm/455/opioidschronicpain.pdf.
23. Federation of State Medical Boards of the United States, Inc. Model policy for the use of controlled substances for the treatment of pain. Adopted May 1, 2004 [monograph on the Internet]. Dallas (TX): Federation of State Medical Boards of the United States; 2004 [cited 2005 Aug 10]. Available from: www.ama-assn.org/ama1/pub/upload/mm/455/fsmbguidelines.pdf.
24. Kaiser Permanente. Care Management Institute. Chronic Pain Guidelines Group. Evidence-based guidelines and technical review for chronic pain management in primary care [monograph on the Intranet]. [Oakland (CA)]: Care Management Institute; 2002, rev May 2004 [cited 2005 Mar 3]. Available from: cl/kp.org/pkc/national/cmi/programs/chronicpain/files/chronicpain 2004.pdf.
25. Pasternak GW. Insights into mu opioid pharmacology: the role of mu opioid receptor subtypes. Life Sci 2001 Apr 6;68(19-20):2213-9.
26. Pasternak GW. Incomplete cross tolerance and multiple mu opioid peptide receptors. Trends Pharmacol Sci 2001 Feb;22(2):67-70.
27. Latta KS, Ginsberg B, Barkin RL. Meperidine: a critical review. Am J Ther 2002 Jan-Feb;9(1):53-68.
28. Whitten CE, Evans CM, Cristobal K. Pain management doesn't have to be a pain: working and communicating effectively with patients who have chronic pain. Perm J 2005 Spring;9(2):41-8.
29. Whitten CE, Cristobal K. Chronic pain is a chronic condition, not just a symptom. Perm J 2005 Summer;9(3):43-51.
30. Schweitzer A. On the edge of the primeval forest & More from the primeval forest: experiences and observations of a doctor in Equatorial Africa. New York: Macmillan Company; 1948.