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linking mechanisms & guidelines
to the realities of clinical practice

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Chronic Pain Management in the Elderly: Linking Mechanisms & Guidelines to the Realities of Clinical Practice

Based on a CME symposium held during the AAPM 21st Annual Meeting in Palm Springs, California, on February 25, 2005, and supported by an educational grant from Endo Pharmaceuticals Inc.

Target Audience

This activity has been designed to meet the educational needs of physicians involved in the management of elderly patients with chronic pain.

Statement of Need/Program Overview

The treatment of chronic pain continues to be challenging, particularly in the elderly, who frequently present with comorbidities and age-related physiologic changes that alter the pharmacokinetics of many analgesic medications. Guidelines recently published by the American Pain Society and The American Geriatrics Society provide an evidence basis for the use of non-steroidal anti-inflammatory agents, anticonvulsants, topical analgesics, tricyclic antidepressants, and opioids to treat persistent pain, both in the elderly and in other patients. Overall, a thorough review of the medications recommended in the guidelines is an important step toward determining a rational approach to the polypharmacy that is frequently required to treat chronic pain effectively for the elderly. This monograph is intended to integrate the current literature with the evidence-based guidelines, and to synthesize a clinical management approach for clinicians treating elderly patients who experience chronic pain.

Educational Objectives

Upon completion of this activity, the participant should be better able to:

- Discuss the prevalence of common types of chronic pain for the elderly: osteoarthritis, low back pain, and neuropathic pain
- Review the rationale for, and clinical advantages and limitations of, common pharmacologic agents used to treat chronic nociceptive, neuropathic, and inflammatory conditions in the elderly
- Review recently published evidence-based guidelines for the treatment of common nociceptive, neuropathic, and inflammatory chronic pain conditions that afflict the elderly
- Describe clinical strategies that incorporate the recently published guidelines and the principles of rational polypharmacy to design a treatment approach that provides efficacy and minimizes side effects

Faculty

Charles E. Argoff, MD (Editor)
Assistant Professor of Neurology
New York University School of Medicine
New York, New York

Director, Cohn Pain Management Center
North Shore University Hospital
Manhasset, New York

Bill H. McCarberg, MD
Assistant Clinical Professor—Voluntary Faculty
University of California, San Diego, School of Medicine
San Diego, California
Founder, Chronic Pain Management Program
Kaiser Permanente
San Diego, California

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PHARMACOTHERAPEUTIC OPTIONS IN PAIN MANAGEMENT

Charles E. Argoff, MD

Common Causes of Chronic Pain in the Elderly: Musculoskeletal Disorders

Chronic pain syndromes such as cancer-related pain, osteoarthritis and other musculoskeletal pain states, postherpetic neuralgia (PHN), painful diabetic neuropathy (PDN), and poststroke pain are common in the geriatric population¹; however, the musculoskeletal disorders—osteoarthritis² and low back pain (LBP)—are the main sources of chronic pain in the elderly. The majority of adults aged older than 55 years exhibit radiographic evidence of osteoarthritis, and the disease is probably the leading cause of functional disability among adults in developed countries.³ Osteoarthritis can lead to the loss of function of the knees and hips primarily, and it affects 9.6% of men and 18% of women aged older than 60 years.⁴ It has been predicted that by the year 2020 osteoarthritis may be the fourth leading cause of disability, due to the growing elderly population.⁴

Musculoskeletal disorders—of which LBP is the most prevalent condition—are the most common causes of severe long-term pain and physical disability.⁴ Overall, LBP has a point prevalence of 4% to 33%⁴; approximately 10 million Americans are disabled by the condition.⁵ Although there are several identifiable acute causes of LBP, the primary antecedent is the natural aging of the disks of the spine (disk degeneration).⁶ Disk degeneration can become evident as early as during one's mid 20s and is nearly universal by age 50 years.⁷ Overall, the prevalence of disk degeneration and facet joint arthritis increases with age.⁸

Disease Processes That Result in Chronic Pain

Osteoarthritis and LBP result from degenerative processes. In particular, osteoarthritis is the result of the progressive degeneration of articular cartilage—the tissue that allows low-friction movement of synovial joints—resulting in dysfunction and pain.⁹ The tissue matrix of the cartilage is produced by chondrocytes that reside there; however, the cells lose their ability to maintain and restore articular cartilage with age.⁹ Similarly, the degeneration of spinal disks that can lead to chronic LBP begins with subtle biochemical alterations, progresses to microstructural changes, and ultimately leads to gross structural alterations.⁶ These changes may occur during the third decade of one's life. At the cellular level, degeneration of the disk is

caused by reduced production of extracellular matrix.⁶ Furthermore, degeneration is promoted by reduced blood flow from the end plate, resulting in lowered nutrient supply to disk cells.⁶ These processes lead to macroscopic changes that include a less distinct boundary between the nucleus and annulus, concentric fissuring and radial tears, and the loss of disk height and turgor.⁶ These disk changes can have the secondary effect of increasing the load on the facets, resulting in cartilage degradation there.⁶ Furthermore, a narrowing disk space within the lumbar vertebrae—more than other types of radiographic evidence⁸—has been strongly associated with LBP.

Disk degeneration includes a broad range of clinical, radiologic, and pathologic processes, and can lead to the deterioration of the facets, ligaments, and muscles of the spine. This can result in somatic pain originating from processes that include the spine and surrounding muscles, ligaments, periosteum, facet joints, blood vessels, and intervertebral disks,⁵ or in radicular pain that stems from neural structures. Although clinicians use procedures such as manual examinations, thorough patient histories, myelograms, dynamic X-rays, computed tomography scans, and magnetic resonance imaging to aid in identification of the origin of musculoskeletal pain, it is often not possible to determine a precise cause. LBP may stem from identifiable etiologies such as compression fractures, herniated disks, spondylolisthesis, tumors, spondylitis ankylopoietica, or infections¹⁰; however, most LBP is considered idiopathic. Since the precise etiology of musculoskeletal pain is often indeterminate, the management of the symptom is complicated, and any 1 therapy is oftentimes not completely effective at providing pain relief. Management of chronic LBP has therefore evolved into a multidisciplinary approach that considers and integrates pharmacotherapy, surgical interventions, physical therapy, and behavioral pain management. These should be integrated early in the disease progression to yield the most successful management approach.

Pain Management for the Elderly: Nonopioid Pharmacotherapies

The World Health Organization (WHO) developed a set of guidelines in 1985¹¹ for managing cancer pain that has since been validated for these patients¹² and then adapted for use with noncancer pain and in special populations.

The elderly population presents with a special set of requirements and limitations that necessitate an adaptation of the World Health Organization (WHO)

recommendations for pain management. Figure 1 lists the types of medications to be used in a stepwise manner as suggested by WHO, with those therapies that should generally not be prescribed for the elderly marked with an “X”. In particular, amounts of acetaminophen and aspirin intake should be limited; amitriptyline should generally be avoided; and propoxyphene should never be prescribed.

Level 3 (severe pain): Strong opioids—morphine, hydromorphone, fentanyl, oxycodone±adjuvants

Level 2 (moderate to severe pain): Acetaminophen plus opioid [hydrocodone, oxycodone, codeine; tramadol±adjuvants, propoxyphene]

Level 1 (mild to moderate pain): Acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2–specific NSAIDs±adjuvants

Figure 1. WHO ladder (adapted for the elderly).

Note: Therapies marked with an “X” are not appropriate for use in the elderly.

The breadth of nonopioid pharmacotherapy options for the management of chronic pain is indicated by the (alphabetical) listing in Table 1, and the following section will provide details on the benefits and limitations of those pharmacotherapies.

Table 1. A List of Commonly Used Nonopioid Pharmacotherapy Options for Chronic Pain

Acetaminophen
 Alpha-adrenergic agents
 Anticonvulsants
 Antidepressants
 Muscle relaxants
 Neuroleptic agents
 NMDA-receptor antagonists
 NSAIDs
 Oral local anesthetics
 Topical analgesics
 Other agents in development
 NMDA=N-methyl-D-aspartate.

Acetaminophen

Acetaminophen is a first-line pharmacotherapy for the relief of chronic pain in the elderly.¹³ However, it is important to minimize acetaminophen use, as too much intake can be problematic. For example, an overdose of acetaminophen can cause liver damage, and the consumption of even approximately 4000 mg daily (taken either 1000 mg 4X, or 650 mg 6X) for adults can have adverse effects in the long term. Furthermore, a lower dose of 2000 mg daily has been recommended by the FDA—especially in older individuals—for patients with concurrent alcohol use or liver disease, or who are taking other medications that potentially could inflict liver damage. Frail elderly who exhibit signs of liver impairment, such as jaundiced skin or eyes, nausea, vomiting, stomach pain, white stool, or black urine, should have their acetaminophen intake minimized. However, determining the total dose taken daily can be difficult for the elderly, as often comorbidities require polypharmacy, and many OTC medications contain acetaminophen. Patients must be reminded regularly not to use an excessive amount of acetaminophen.

Alpha-adrenergic Agents

Alpha-adrenergic agents are one of the most under-used types of pharmacotherapies available for pain. Epidurally administered clonidine is FDA approved for the indication of chronic neuropathic pain and has been shown to be effective in certain patients.¹ Also, a structurally similar agent that acts as an alpha-2–receptor agonist—the muscle relaxant tizanidine¹⁴—has a 30-year history of usage as an analgesic outside of the United States. A multicenter, randomized, controlled trial conducted in the United Kingdom demonstrated the efficacy of tizanidine usage for the relief of acute LBP.¹⁵ No serious drug-related adverse effects were reported, although drowsiness was observed in 22% of patients administered tizanidine.¹⁵ Tizanidine has also been administered for the effective relief of chronic headache pain,¹⁶ chronic cluster headache,¹⁴ and chronic tension headache.¹⁷

Anticonvulsants

In general, anticonvulsant drugs are effective treatments for neuropathic pain.¹⁸ However, the agents developed within the past decade, or “second generation”—such as gabapentin and topiramate—have a safer side-effects profile for the geriatric population.¹⁸ Many agents within this class have FDA approval for the treatment of pain and/or headache, including carbamazepine (trigeminal neuralgia), divalproex

sodium (migraine headache), gabapentin (PHN), pregabalin (PHN and pain associated with PDN), and topiramate (migraine headache). Also, other agents, such as phenytoin, lamotrigine, zonisamide, and oxcarbazepine have been examined with varying degrees of study quality and outcome for off-label uses in pain management. Furthermore, many of these pharmacotherapies have demonstrated efficacy for neuropathic pain disorders, such as lamotrigine's use with human immunodeficiency-associated neuropathy, trigeminal neuralgia pain, central poststroke pain, and PDN, and the use of oxcarbazepine and carbamazepine for the treatment of trigeminal neuralgia pain. Trials have shown efficacy at reducing the pain of PDN by treatment with carbamazepine, phenytoin, gabapentin, and pregabalin, as well. Commonly, anticonvulsants are used for the treatment of chronic musculoskeletal pain and the pain associated with osteoarthritis, although none are FDA approved for this indication.

Antidepressants

Effective management of chronic pain in the elderly—especially neuropathic pain—oftentimes involves antidepressants.^{13,18} The analgesia provided by this drug class is independent of the antidepressant effect, and may be more potent in those therapies that target multiple receptors or predominantly noradrenergic receptors rather than serotonin receptors.¹⁸ Use of the tricyclic antidepressants—amitriptyline, nortriptyline, and desipramine—has become a traditional approach to the management of chronic pain.¹⁸ In particular, both amitriptyline and its metabolite nortriptyline have established analgesic efficacy for managing neuropathic pain. However, individuals aged older than 60 years should be prescribed nortriptyline, because of its safer adverse events profile. Amitriptyline is contraindicated in the elderly due to the possibility of cardiac adverse events and

anticholinergic side effects, among others. Several novel antidepressants—bupropion,¹⁹ venlafaxine,²⁰ and duloxetine²¹—have demonstrated efficacy at reducing neuropathic pain, as well.¹⁸ Most notably, duloxetine is the only FDA-approved pharmacotherapy of this type, with an indication for the treatment of PDN pain. Studies of selective serotonin reuptake inhibitors have not reported efficacy comparable to traditional tricyclics. A more complete listing of antidepressants used for the treatment of chronic pain appears in Table 2, and Table 3²² lists recommendations for using tricyclic antidepressants, as well as other nonopioid pharmacotherapies, with elderly patients.

Muscle Relaxants

Muscle relaxants are a diverse group of drugs that have been used to reduce the pain often associated with muscle spasm and that can have sedative effects. Cyclobenzaprine is a centrally acting muscle relaxant that is structurally similar to the tricyclic antidepressant class. It was determined to be efficacious and safe for the treatment of acute LBP in 2 recent randomized, controlled clinical trials.²³ However, the side effects of cyclobenzaprine include the anticholinergic-related adverse events typical of amitriptyline, as well as fatal cardiac arrhythmias. It should not be prescribed for the elderly. A precursor of meprobamate, carisoprodol is another centrally active muscle relaxer. Although some evidence indicates that carisoprodol is efficacious for the relief of acute LBP and neck pain relative to placebo,²⁴ the pharmacotherapy can induce both physical and psychologic dependency, as well as sedation and drowsiness. Furthermore, limited or inconsistent evidence exists for the use of the muscle relaxants methocarbamol, metaxalone, and orphenadrine citrate for muscle spasticity and associated pain.²⁴ Metaxalone is a non-sedating medication that can be used in the elderly with proper precautions (such as taking liver function measurements at the start of therapy). Orphenadrine is an analog of diphenhydramine that was investigated for use with spinal cord injury patients. A study of 11 patients indicated that intravenous administration of orphenadrine could reduce spastic hypertonia in paraplegics.²⁵ Orphenadrine has anticholinergic side effects and can induce rare aplastic anemia, suggesting that it should not be used for elderly patients.

Neuroleptic Agents

Fluphenazine is a neuroleptic agent that likely inhibits central dopaminergic pathways to exert its effects. Pilot studies more than 2 decades ago suggested that fluphenazine in combination with amitriptyline could

Table 2. Antidepressants

| TRICYCLIC | SSRI | OTHER |
|---------------|-------------|-------------|
| Amitriptyline | Fluoxetine | Venlafaxine |
| Desipramine | Paroxetine | Duloxetine* |
| Doxepin | Sertraline | Trazodone |
| Imipramine | Fluvoxamine | Bupropion |
| Nortriptyline | Citalopram | |

*FDA approved for pain

Table 3. Nonopioid Systemic Pharmacotherapy for Persistent Pain Management in the Elderly²²

| Drug | Starting Dose* | Usual Effective Dose (Maximum Dose) | Titration | Comments |
|--|-------------------------------|-------------------------------------|-----------------|--|
| NONOPIOIDS | | | | |
| Acetaminophen | 325 mg q 4 h– 500 mg q 6 h | 2–4 g/24 h (4 g/24 h) | after 4–6 doses | Reduce maximum dose 50%–75% in patients with hepatic insufficiency; history of alcohol abuse |
| Tricyclic antidepressants†: desipramine nortriptyline | 10 mg hs | 25–100 mg hs (variable) | after 3–5 days | Significant risk of adverse effects in older patients; anticholinergic effects |
| Anticonvulsants –carbamazepine | 100 mg qd | 800–1200 mg/24 h (2400 mg/day) | after 3–5 days | Monitor LFTs, CBC, BUN/ serum creatinine, electrolytes |
| –clonazepam | 0.25–0.5 mg hs | 0.05–0.2 mg/kg/day (20 mg) | after 3–5 days | Monitor sedation, memory, CBC |
| –gabapentin | 100 mg hs | 300–900 mg tid (3600 mg) | after 1–2 days | Monitor sedation, ataxia, edema |
| Mexiletine | 150 mg | 150 mg tid–qid (variable) | after 3–5 days | Avoid use in patients with conduction block, bradyarrhythmia; monitor ECG |
| BUN=blood urea nitrogen CBC=complete blood cell count ECG=electrocardiogram LFT=liver function test *Oral dosing unless otherwise specified. †Amitriptyline is not recommended. | | | | |

reduce the pain associated with PDN.²⁶ The authors of that small study reported that the therapy was safe and effective even for patients with mild to moderate renal insufficiency.²⁷ However, a more recent controlled study of 49 PHN patients indicated that amitriptyline alone induced a statistically significant decrease in pain, which was not boosted by the addition of fluphenazine.²⁸ Also, fluphenazine is not recommended for the elderly, as the anticholinergic activity of the therapy could result in complications such as paralytic ileus.

N-methyl-D-aspartate–Receptor Antagonists

The *N*-methyl-D-aspartate (NMDA) receptor is well studied in the field of neuroscience. It is 1 of the receptors that is bound by the excitatory neurotransmitter glutamate. Increased agonist activity at the NMDA receptor has been implicated in a number of neurologic conditions, including chronic pain, dementia, and ischemic brain injury associated with cerebrovascular disease. Research on the potential role of the NMDA receptor in pain transmission indicates that there is intracellular crosstalk with the μ -opioid receptor through the activation of protein kinase C.

These interactions may serve to provide a homeostatic mechanism to balance both pain transmission and pain control. These interactions also suggest that NMDA-receptor antagonists may potentiate the analgesic benefit of μ -opioid analgesics, as well as provide analgesia through the direct blockade of the actions of the neurotransmitter glutamate. Animal studies have suggested that activation of the NMDA receptor may play a significant role in the development of opioid tolerance. Ultimately, the inhibition of NMDA receptors could help minimize the changes within those signaling networks that can lead to hyperalgesia and opioid tolerance.²⁹ However, the currently known and available NMDA receptor antagonists have demonstrated limited, if any, clinical utility.

The NMDA antagonist dextromethorphan has exhibited efficacy at relieving neuropathic pain only when administered at high doses³⁰—levels that would be intolerable for the elderly. Similarly, ketamine has the same restrictions, although it can be effective when administered intravenously. The *D*-isomer of the opioid methadone has NMDA receptor antagonist activity and is reported to reduce morphine tolerance and NMDA-induced hyperalgesia.³¹ This suggests that

a racemic mixture of methadone may be one of the best opiates to consider prescribing for pain, except in the elderly population because of its adverse effects. In a randomized, controlled trial, the antiviral and parkinsonian medication amantadine has been shown to be an effective acute treatment when administered intravenously in patients experiencing surgical neuropathic pain associated with cancer.³² However, this NMDA antagonist may not be useful for the treatment of chronic pain in the geriatric population. The NMDA antagonist memantine is the newest FDA-approved medication for Alzheimer's disease.³³ It exerts its pharmacologic effect by blocking excessive NMDA-type glutamate receptor activity, while allowing normal physiologic activity at those receptors. Clinical data indicate that memantine is well tolerated; further studies are being conducted to assess its usefulness for the treatment of other neurologic disorders, such as severe neuropathic pain.³³ Finally, recent data suggest that the analgesic activity of amitriptyline for the relief of chronic tension-type headache may in part be due to its NMDA-antagonist activity, as well as other mechanisms, including sodium channel blockade.³⁴ Regardless, as a consequence of its adverse effect profile, amitriptyline is not recommended for use in geriatric patients.

Nonsteroidal Anti-inflammatory Drugs

Cyclooxygenase-2 (COX-2)-specific inhibitor therapies had been widely prescribed to the elderly for pain relief due to osteoarthritis and rheumatoid arthritis.² Although they do not provide more effective pain relief than nonspecific COX inhibitors, COX-2-specific therapies (when taken *without* concurrent aspirin use) had been theorized to induce fewer side effects, most significantly fewer gastroduodenal adverse events than traditional NSAIDs.² However, further research indicated that high doses of COX-2 inhibitors may (similarly to standard NSAIDs) induce renal failure, hypertension, and exacerbation of cardiac failure.²

The safety of the COX-2-specific inhibitor rofecoxib was evaluated following the publication of the Vioxx Gastrointestinal Outcomes Research study in *The New England Journal of Medicine* in November 2000.^{35,36} The data suggested that there was a significant increase in the risk of myocardial infarction in patients treated with rofecoxib, although it is well tolerated and efficacious for conditions such as osteoarthritis in the elderly.³⁷ A follow-up placebo-controlled trial confirmed the cardiovascular risk of rofecoxib, leading to its voluntary withdrawal from the market in September 2004. In February 2005, the US Food and

Drug Administration (FDA) Drug Safety and Risk Management Committee overwhelmingly agreed that COX-2 inhibitors significantly increase the risk of cardiovascular disease, suggesting that celecoxib and valdecoxib were implicated as well. More recently, the FDA issued requests for labeling changes for both prescription and over-the-counter (OTC) NSAIDs. Manufacturers of OTC NSAIDs are being asked to provide more specific information about potential gastrointestinal (GI) and cardiovascular (CV) risks associated with use on their packaging instructions. Furthermore, the FDA has requested the withdrawal of valdecoxib from the market due to an unfavorable risk-to-benefit-profile, and requested the inclusion of a boxed warning on the celecoxib label.

Oral Local Anesthetics

To date, studies of the use of oral local anesthetics indicate that they do not provide effective relief of pain, despite attempts to replicate the benefits of intravenous lidocaine. A single bolus or lidocaine infusion can be an extremely effective approach to managing neuropathic and nonneuropathic pain. A randomized trial of the oral anesthetic mexiletine reported pain reduction relative to the placebo (by visual analog scale), without significant side effects.³⁸

Topical Analgesics

Topical analgesics are a safe and effective alternative when managing chronic pain of a localized nature. These therapies primarily remain at the site of application, affecting the skin, soft tissues, and peripheral nerves therein. In contrast, the systemic distributions of transdermal, oral, or parenteral therapies have a higher potential to generate systemic side effects and drug-drug interactions than topical agents. However, there are no currently FDA-approved prescription topical pharmacotherapies for the relief of musculoskeletal pain such as osteoarthritis. There have been trials investigating the use of topical aspirin preparations, capsaicin, lidocaine patch 5%, tricyclic antidepressants, NSAIDs, and opioids for chronic musculoskeletal pain relief. Capsaicin was found to have moderate to poor efficacy for control of chronic musculoskeletal or neuropathic pain.³⁹ A randomized, controlled study of 200 patients experiencing chronic neuropathic pain indicated that topical capsaicin, the tricyclic antidepressant doxepin (cream), or a combination of the 2, significantly reduced pain to a similar extent, although the combination had a more rapid onset.⁴⁰ However, in the United States, chronic pain is not an FDA-approved indication for doxepin. The

topical NSAID diclofenac also, is not approved by the FDA, but has been studied in several randomized, controlled trials. Topical diclofenac was found to be more effective than placebo^{41,42} and to provide equivalent relief compared with oral diclofenac⁴³ for the treatment of knee osteoarthritis. This agent was found to be as effective as oral diclofenac for the relief of temporomandibular joint pain as well, without inducing adverse systemic effects.⁴⁴ Also, significantly reduced pain intensity and minimal side effects have been reported for the treatment of osteoarthritis and LBP with the lidocaine patch 5% in 3 open-label pilot studies.⁴⁵⁻⁴⁷ A recent *Geriatrics* publication recommended the topical analgesics, lidocaine patch 5% and capsaicin as options for pain associated with rheumatologic illnesses in the elderly population.⁴⁸

Other Investigational Analgesics

The neurotoxin botulinum toxin type A (BoNT/A) is reported to be efficacious for several disorders of involuntary muscle contraction and is being investigated as a novel treatment for pain associated with migraine and other types of chronic headaches.⁴⁹ BoNT/A is known to inhibit the release of acetylcholine at cholinergic synapses, which at the neuromuscular junction results in a flaccid paralysis; however, other newly discovered mechanisms of the toxin—for example, its effect on glutamate transmission, as well as the reduction of substance P and calcitonin gene-related peptide release—may be more relevant with respect to its analgesic effects. Several open-label studies and 3 placebo-controlled trials reported decreased migraine frequency and severity following BoNT/A injection, with a small frequency of transient, minor side effects.⁴⁹ BoNT/A was found to be efficacious for the relief of chronic LBP, as well, in a randomized, placebo-controlled study of 31 patients.⁵⁰

Thalidomide is also under investigation for the management of chronic pain.

Pain Management for the Elderly: Opioid Pharmacotherapies

The proven efficacy of opioids for the reduction of pain from several sources, including both acute cancer-related and chronic, noncancer-related pain, has encouraged the growing recognition that opioids are essential for the management of chronic pain.⁵¹ The potential risks of opioid use are serious but manageable, especially with the plethora of guidelines available from sources such as the FDA, Federation of State Medical Boards, and the American Pain Society.

The main goal with opioid therapy is to maximize symptom relief and functional improvement for patients in chronic pain, while minimizing the risk of addiction, diversion, and side effects.

Opioids can be prescribed in short-acting form (such as preparations of morphine sulfate, codeine, hydrocodone, oxycodone, hydromorphone, oxymorphone, or fentanyl) or in longer-acting formulations (such as methadone, sustained-release morphine, sustained-release oxycodone, and transdermal fentanyl). At present, there is insufficient evidence to indicate that longer-acting opioids have better efficacy or safety profiles⁵² than short-acting agents, although it has been suggested that prescribing longer-acting formulations may result in improved compliance and greater overall ease of use.

The efficacy of opioids for chronic, noncancer pain has been established by many placebo or active-controlled trials of codeine,^{53,54} oxycodone,^{55,56} morphine,⁵⁷ oxymorphone,⁵⁸ and fentanyl.⁵⁹ In sum, there is no shortage of data describing the benefits of opioids for the relief of chronic pain. However, although important for all of pharmacotherapy, it is especially important to assess and document the outcome of treatment for pain with opioids by considering the following 4 areas for each patient: analgesia (Was the patient relieved of pain?), activities of daily living (Was the patient able to return to typical daily activities?), adverse effects (Did the treatment induce disruptive side effects?), and aberrant drug-taking behaviors (Did the patient develop a potentially abusive habit with the medication?).

Keep in mind that several opioid analgesics should not be used in the geriatric population. Propoxyphene has a toxic active metabolite and a long half-life, and therefore it is not recommended for elderly patients because of its adverse effects. Methadone should also be prescribed with caution in the elderly. The agonist-antagonists nalbuphine, pentazocine/naloxone hydrochlorides, and butorphanol tartrate are not recommended for the elderly. Finally, meperidine has a toxic metabolite that contraindicates it in the geriatric population, because of possible deleterious effects on the renal, hepatic, and gastrointestinal function.

Conclusion

Numerous pharmacotherapeutic options are available for the management of chronic pain in the elderly. The best analgesic approach can be optimized through the proper evaluation of a patient, including assessing pain relief, adverse effects, and the cost/

benefit ratio of a therapy. Overall, the best way to manage chronic pain in elderly patients involves an integrated strategy that makes use of current developments and research in pharmacologic therapies, both opioid and nonopioid, as well as adjuvants, interventional techniques such as epidurals, physical therapies (massage, rehabilitation, transcutaneous electrical nerve stimulation), behavior modification strategies, and surgical therapies.

MANAGING PERSISTENT NEUROPATHIC PAIN IN THE ELDERLY

Bill H. McCarberg, MD

In the United States, there are currently approximately 34 million people aged 65 years or older.⁶⁰ In this sizable geriatric population, pain is the most common symptom described during physician consultations.⁶⁰ Typically, the causes of pain are musculoskeletal disorders—such as low back pain (LBP) and osteoarthritis—as well as pain resulting from fractures and neuropathic disorders.⁶⁰ Yet, pain is undertreated in the elderly, with the incidence varying from 25% to 50% in adult communities and 45% to 85% in long-term care facilities.⁶⁰ There is a tendency for pain to go unchecked in the elderly; reasons are enumerated in the following section.

Impediments to Managing Chronic Pain in the Elderly

There are multiple barriers to providing chronic pain care for the geriatric population. Some difficulties in managing chronic pain arise because of inherent barriers within the patient. Often it is difficult to obtain a pain score, as patients can present with cognitive deficits and auditory and/or visual impairment that hamper the evaluation process. Also, some of the pain measurement techniques that are available do not yield reliable results when used with the elderly. Geriatric patients prefer word scales rather than rating scales that use numbers. The Wong-Baker FACES Pain Rating Scale⁶¹ is particularly problematic for use with elderly men. The worst pain on the Wong-Baker scale is denoted by a crying face; however, older men do not identify with crying as being a component of their pain. Therefore, elderly men do not rate their pain as a 10 on the Wong-Baker scale. Furthermore, many elderly patients view pain as part of the normal aging process.⁶⁰ Often, they refrain from mentioning pain to their physician, to avoid being seen as a “complainer”.

Medical conditions often progress differently in the elderly than in younger populations. For example, a

younger patient afflicted by a herpes zoster outbreak generally does not experience chronic neuropathic pain (pain that persists 2 months or more after the rash has healed) as an elderly patient might. Elderly patients presenting with a new condition often have multiple comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease [COPD], or congestive heart failure) already existent. Improving even a seemingly minor aspect of their life or functioning—such as being able to get out of bed unaided—can make a significant life-quality difference for the elderly, more so than with younger generations. Therefore, a minor improvement in pain can result in a major difference in quality of life (QOL). For example, especially for the elderly, pain relief can have a beneficial impact on other comorbidities, including anxiety, depression, sleep disturbances, ambulation, socialization ability, or vitality.

Physicians have obstacles as well that make providing adequate pain relief for the geriatric population more complicated. For example, there are misconceptions about how the elderly feel pain.⁶⁰ It is widely believed that the elderly do not experience pain at the same intensity as younger populations.⁶⁰ In a model of acute pain, this is true—when an elderly subject is administered a shock or pressure, the pain intensity experienced by the subject is diminished relative to a younger subject. However, when the elderly *do* sense pain, the duration is often extended, the sensation becomes hard for them to describe, and it leaves a stronger psychologic impact. Also, when treating geriatric patients, physicians have stronger concerns about prescribing medications with side effects that include diminished cognition, gait disturbance (possibly leading to falling), and constipation, than they have with younger patients. These issues may make physicians less aggressive about finding an optimal pain control therapy for the elderly.

Aging often induces pharmacokinetic modifications to drug responses, making it necessary to modify the types and doses of prescriptions for the elderly. Renal-excreted and hepatic-excreted medications are not always completely cleared and tend to have longer half-lives in the elderly.⁶² The potential for generating higher concentrations of medications for lengthened periods can increase the likelihood of side effects, as well as increase their duration and intensity. The potential for a larger side-effect profile can limit the physician's willingness to increase the dosage, even if a medication is not providing effective pain relief. Also, the central nervous system of the elderly can have a higher sensitivity to medications.

Recommendations for Managing Neuropathic Pain in the Elderly

It is important to establish reasonable treatment goals when managing elderly patients experiencing chronic pain. Pain syndromes—such as back pain, complex regional pain syndrome, and fibromyalgia syndrome—are similar to other chronic diseases, in that they are not “cured.”⁶³ Instead, the main objective for interventions should be to lessen pain, in order to improve physical functioning, reduce psychologic stress, and improve overall QOL. Positive outcomes should be emphasized—not just the initial results of a treatment—and regular follow-up with patients to maintain ongoing lifestyle changes should be expected.⁶³

Members of the faculty of the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain published an article in the *Archives of Neurology* that detailed specific guidelines for treating neuropathic pain (Table 4).⁶⁴ Their first-line recommendations were for the 2 therapies that were US Food and Drug Administration (FDA) approved for treating postherpetic neuralgia (PHN) at the time

of publication: gabapentin and lidocaine patch 5%, as well as for opioid analgesics, tramadol, and antidepressants.⁶⁴ Since the article was published in 2003, 2 new pharmacotherapy options were approved with indications for neuropathic pain. Pregabalin received indications for neuropathic pain associated with painful diabetic neuropathy (PDN) and PHN, while duloxetine was approved for diabetic peripheral neuropathic pain. Also, carbamazepine was FDA approved for the treatment of trigeminal neuralgia, before it was approved as an anticonvulsant; it was one of the first approved therapies for neuropathic pain. Likely the safety profile of an analgesic therapy will be the crucial factor in determining the optimal therapy for a patient. More recent guidelines from the American Academy of Neurology were published in 2004 (Table 5).⁶⁵

Typically, primary care physicians manage many of the chronic conditions experienced by the elderly—such as atherosclerotic cardiovascular disease (ASCVD), stroke, hypertension, diabetes, COPD, and asthma—simply because of the economics of medicine in the United States. Similarly, primary care physicians handle most chronic pain cases in the elderly; therefore, they need to be informed about the typical obstacles

Table 4. First-line Medications for Neuropathic Pain⁶⁴

| Medication | Beginning Dosage | Titration | Maximum Dosage | Duration of Adequate Trial |
|--|--|---|--|--|
| Gabapentin | 100–300 mg every night or 100–300 mg 3 times daily | Increase by 100–300 mg 3 times daily every 1–7 d as tolerated | 3600 mg/d (1200 mg 3 times daily); reduce if low creatinine clearance | 3–8 wk for titration plus 1–2 wk at maximum tolerated dosage |
| 5% Lidocaine patch | Maximum of 3 patches daily for a maximum of 12 h | None needed | Maximum of 3 patches daily for a maximum of 12 h | 2 wk |
| Opioid analgesics* | 5–15 mg every 4 h as needed | After 1–2 wk, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed | No maximum with careful titration; consider evaluation by pain specialist at dosages exceeding 120–180 mg/d | 4–6 wk |
| Tramadol hydrochloride | 50 mg once or twice daily | Increase by 50–100 mg/d in divided doses every 3–7 d as tolerated | 400 mg/d (100 mg 4 times daily); in patients older than 75 y, 300 mg/d in divided doses | 4 wk |
| Tricyclic antidepressants (eg, nortriptyline hydrochloride or desipramine hydrochloride) | 10–25 mg every night | Increase by 10–25 mg/d every 3–7 d as tolerated | 75–150 mg/d; if blood level of active drug and its metabolite is <100 ng/mL, continue titration with caution | 6–8 wk with at least 1–2 wk at maximum tolerated dosage |

*Dosages given are for morphine sulfate.

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encountered in this special population, as detailed in the previous section. Despite the available detailed guidelines, primary care physicians often prescribe ibuprofen for neuropathic pain. Furthermore, tricyclic antidepressants (TCAs) tend to be recommended (following an electrocardiogram [EKG]) because of the randomized, controlled evidence available and the relatively low cost of the medications. The risk of QRS prolongation and cardiac arrhythmias is large enough within the elderly population that an EKG before TCA treatment is recommended as the standard of care.

Treatments for Neuropathic Pain

Topical Agents

As previously alluded to, topical analgesia is now considered a first-line therapy for neuropathic pain because of its demonstrated efficacy in randomized controlled trials and safety profiles that offer clinical advantages compared with systemic agents.⁶⁴ The lidocaine patch 5% is indicated for localized pain associated with PHN. Lidocaine binds to open sodium channels, inhibiting depolarization and reducing neurotransmitter release. Three randomized controlled trials of patients experiencing PHN demonstrated significantly reduced pain without systemic side effects.⁶⁶⁻⁶⁸ Topical aspirin⁶⁹ and nonsteroidal anti-inflammatory drug preparations (dissolved in chloroform or ether) have been reported to be an effective means of reducing pain from PHN. Interestingly, the analgesia provided by topical aspirin may depend on a

mechanism other than its anti-inflammatory activity, such as the stabilization of membrane potentials of nociceptors.⁶⁹ Also, the chili pepper extract—capsaicin—has been used as a treatment for pain associated with arthritis, cystitis, human immunodeficiency virus, and PDN.⁷⁰ However, the application of capsaicin—especially at high concentrations—can be extremely painful for patients experiencing allodynia. A eutectic mixture of lidocaine 2.5% and prilocaine 2.5% (administered as a topical cream) is indicated for use on normal, intact skin for local anesthesia.

Tricyclic Antidepressants

Although there are no tricyclic antidepressants approved by the FDA for the treatment of PHN, studies of amitriptyline, nortriptyline, and desipramine have indicated these therapies can provide effective pain relief. A randomized, controlled trial of 58 patients with PHN found that relative to the placebo, significant pain relief could be achieved at a dose of 150 mg amitriptyline, taken daily ($P < .01$).⁷¹ However, amitriptyline, according to The American Geriatrics Society, should not be prescribed for patients aged 60 years and older. Also, propoxyphene—although commonly prescribed—should not be used by geriatric patients, as it offers little additional analgesia over acetaminophen alone and induces the side effects of opioids.⁷² A head-to-head, randomized, crossover trial of nortriptyline and amitriptyline indicated that both provide similar

Table 5. American Academy of Neurology-Recommended Treatment Categories for Postherpetic Neuralgia⁶⁵

| Group 1: Medium to high efficacy, good strength of evidence, and low level of side effects | Group 2: Lower efficacy than those listed in group 1, or limited strength of evidence, or side-effect concerns | Group 3: Evidence indicating no efficacy compared to placebo | Group 4: Reports of benefit limited to class IV studies |
|---|--|---|--|
| Gabapentin Lidocaine patch Oxycodone or morphine sulfate, controlled release Pregabalin Tricyclic antidepressants | Aspirin in cream or ointment Capsaicin, topical Methylprednisolone, intrathecal* | Acupuncture Benzhydramine cream Dextromethorphan Indomethacin Lorazepam Methylprednisolone, epidural Vincristine iontophoresis Vitamin E Zimelidine | Biperidin Carbamazepine Chlorprothixene Cryocautery Dorsal root entry zone lesion Extract of <i>Ganoderma lucidum</i> He:Ne laser irradiation Ketamine Methylprednisolone, iontophoresis Morphine sulfate, epidural Nicardipine Piroxicam, topical Stellate ganglion block Triamcinolone, intralesional |

*While there were no severe adverse effects in the reviewed studies, there is potential for chemical meningitis and arachnoiditis with the use of intrathecal methylprednisolone. Methylprednisolone is not approved by the US FDA for intrathecal use in this indication. The concurrent use of intrathecal lidocaine carries the risk of hypotension and respiratory depression. Therefore, these injections are best given by experienced medical personnel in a hospital setting.

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analgesia, but nortriptyline induces fewer adverse effects.⁷³ Desipramine was also found to provide statistically significant pain relief compared with placebo in a randomized trial of 26 patients with PHN.⁷⁴ As geriatric patients tend to be more frail and have a concomitant medical illness, they generally are more sensitive to the potentially toxic side effects of tricyclic antidepressants.⁷⁵ It is essential to make sure that the therapeutic benefits outweigh the adverse events, which commonly include blurred vision, cognitive changes, constipation, dry mouth, orthostatic hypotension, sedation, sexual dysfunction, tachycardia, and urinary retention.^{75,76}

Overall, tertiary-amine pharmacotherapies (such as amitriptyline and doxepin) have stronger anticholinergic effects than secondary-amine medications (including desipramine and nortriptyline). Desipramine has the least anticholinergic and sedative effects of the first-generation tricyclic antidepressants,⁷⁴ and along with nortriptyline is likely the best therapy within the drug class for the elderly population.⁷⁵

Other Antidepressants

Other types of antidepressant medications prescribed for chronic pain are selective serotonin reuptake inhibitors (SSRI) and selective serotonin and norepinephrine reuptake inhibitors (SSNRI). Paroxetine is an SSRI that has been studied in a randomized, double-blind trial for treatment of PDN. The head-to-head comparison with imipramine reported that 40 mg paroxetine per day significantly reduced the symptoms of PDN.⁷⁷ The SSNRIs venlafaxine and duloxetine have demonstrated efficacy for neuropathic pain relief as well. A randomized, controlled trial of venlafaxine found that it was an effective and safe treatment for PDN.²⁰ However, there is a high rate of hypertension for patients administered the dosage that is effective at relieving neuropathic pain (175 mg–220 mg). Geriatric patients often exhibit hypertension; therefore, medications that exacerbate the condition may not be recommended. Duloxetine has not been found to induce hypertension, and it is the only antidepressant approved by the FDA for PDN pain. A recent trial demonstrated statistically significant improvement of the duloxetine experimental group over the placebo group in a randomized, controlled trial of 457 patients experiencing PDN without clinical depression.²¹ Furthermore, another study considered the long-term impact of treatment for PDN with duloxetine and found a similar rate of adverse events to patients administered routine care.⁷⁸ However, the effective dose of duloxetine (60 mg) can induce nausea; therefore, treatment

is typically initiated at a 20-mg dosage to allow patients to acclimate to the therapy.

Finally, bupropion is a second-generation antidepressant medication that specifically inhibits norepinephrine reuptake and weakly inhibits dopamine reuptake.¹⁹ A randomized, placebo-controlled trial of patients administered bupropion-sustained release (SR) for neuropathic pain demonstrated significant pain relief and a decrease in QOL interference.¹⁹

Anticonvulsant Therapies

Gabapentin has been recommended as a first-line therapy for neuropathic pain⁶⁴ and is frequently prescribed by primary care physicians for relief of chronic pain associated with PHN. It is 1 of 3 anticonvulsant therapies approved by the FDA, along with carbamazepine for trigeminal neuralgia and pregabalin for PDN and PHN. Gabapentin and pregabalin both target α -2- δ voltage-gated calcium-channel receptors to exert their analgesic effect. There are 13 published randomized, controlled, clinical trials of gabapentin for chronic neuropathic pain of various origins, including Complex Regional Pain Syndrome type I, spinal cord injury, postmastectomy, and PDN. A randomized, controlled trial of 334 patients with PHN demonstrated that the group treated with gabapentin had a significant reduction in pain intensity and an improvement in QOL.⁷⁹ Treatment of PDN patients with pregabalin induced significant improvements in pain scores and sleep interference scores over the placebo group in a randomized, double-blind trial.⁸⁰ There are other anticonvulsant therapies that have been effectively used to treat neuropathic pain, based on published, randomized, controlled trial data, or clinical anecdotes and case series.

Tramadol

Tramadol has a combined mechanism of action that includes the weak inhibition of secretion and norepinephrine reuptake as well as μ -opioid receptor binding. It has been recommended as a first-line agent for the treatment of neuropathic pain and is relatively inexpensive.⁶⁴ Tramadol was found to effectively relieve pain and allodynia associated with PDN in a randomized, controlled study.⁸¹

Opioids

Although the adverse-events profile of opioid therapies warrants consideration before prescribing, several studies have indicated that opioid therapies can relieve neuropathic pain. Intravenous fentanyl has been found to be effective treatment for nonmalignant neuropathic pain

Summary based on 56 blinded RCTs:

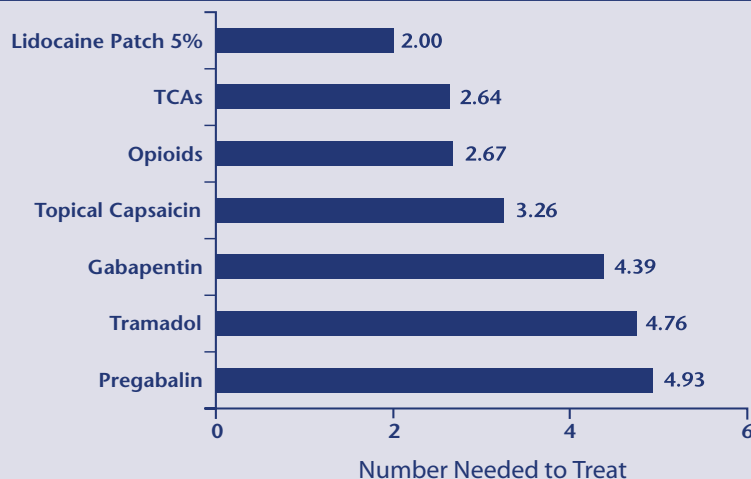


Figure 2. Analgesic therapy in PHN: a quantitative systematic review.⁸²

disorders⁸³; intravenous morphine⁸⁴ and controlled-release oxycodone⁸⁵ can relieve pain associated with PHN; and oral morphine has effectively been administered for phantom limb pain.⁸⁶

A measure of absolute risk, or the numbers needed to treat (where numbers needed to treat is the average number of patients that a clinician would need to treat in order to prevent one adverse outcome), for all agents discussed is indicated in Figure 2.

Conclusion

Regarding the elderly, it is especially important to balance treatment, common conditions, such as pain,

anxiety, depression, and sleep disorders, with resultant effect on functionality. The efficacy of a therapy must be considered along with the possible side effects and drug-drug interactions. The pharmacokinetics of drugs in the elderly population often make modifying the maximum dosages of therapies imperative and make a consideration of the exacerbation of comorbidities essential. Furthermore, the elderly respond to pain and pain therapies differently. An intervention can have an enormous impact on the functionality of an elderly patient—even with only a small change in pain intensity—thus making the therapy a success.

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Chronic Pain Management in the Elderly:

Linking Mechanisms & Guidelines to the Realities of Clinical Practice

POST-TEST

To obtain a certificate of completion, you must complete the post-test by selecting the best answer to each question, complete the evaluation form, and mail to the Postgraduate Institute for Medicine. At least 7 of the 10 answers must be correct to obtain a certificate of completion. Be sure to circle the best answer on the answer key provided on the evaluation form.

- At the cellular level, the degeneration of back disks is caused by:
 - Increased disk height
 - Reduced production of extracellular matrix
 - Increased blood flow to the end plate
 - Chondrocyte overactivity
- Which of the following methods of delivery rarely has/have systemic effects or drug interactions?
 - Topical
 - Transdermal
 - Parenteral
 - Both A and B
- Which of the following antidepressants may have the highest risk of inducing adverse effects within the geriatric population?
 - Amitriptyline
 - Duloxetine
 - Nortriptyline
 - Bupropion
- Which of the following pharmacotherapies has/have anticholinergic activity, making it/them hazardous for use with the elderly?
 - Cyclobenzaprine
 - Fluphenazine
 - Celecoxib
 - Both A and B
- Which of the following opioids has toxic metabolites that may be deleterious to the liver?
 - Methadone
 - Fentanyl
 - Meperidine
 - Tramadol
- Age-induced functional changes in the elderly do NOT affect:
 - The time it takes for the liver and kidneys to metabolize pharmacologic agents
 - The concentration of a pharmacologic agent required to exert an effect
 - The sensitivity of the central nervous system to pharmacologic agents
 - None of the above
- The clinical advantage(s) of topical agents in the treatment of neuropathic pain is/are:
 - Significantly increased efficacy over oral analgesics
 - A better adverse events profile
 - It is the only method to reduce allodynia.
 - All of the above
- The lidocaine patch 5% provides analgesia for neuropathic pain by:
 - Protecting allodynic skin
 - Releasing lidocaine locally for the inhibition of sodium channels located there
 - Reducing muscle spasms
 - Both A and B
- Which of the following is/are FDA approved for both diabetic neuropathy and depression?
 - Duloxetine
 - Paroxetine
 - Bupropion
 - All of the above
- Which of the following has selective serotonin and norepinephrine reuptake inhibition ability and μ -opioid agonist activity?
 - Morphine
 - Venlafaxine
 - Gabapentin
 - Tramadol





EVALUATION FORM

Chronic Pain Management in the Elderly:

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Project ID: 3184-ES-14 Expiration Date: November 30, 2006

Postgraduate Institute for Medicine respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form.

You must complete this evaluation form to receive acknowledgement of participation for this activity.

Please respond to the following statements by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

Extent to Which Program Activities Met the Identified Objectives

After this activity, the participant should be better able to:

- Discuss the prevalence of common types of chronic pain for the elderly: osteoarthritis, low back pain, and neuropathic pain 5 4 3 2 1
- Review the rationale for, and clinical advantages and limitations of, common pharmacologic agents used to treat chronic nociceptive, neuropathic, and inflammatory conditions in the elderly 5 4 3 2 1
- Review recently published evidence-based guidelines for the treatment of common nociceptive, neuropathic, and inflammatory chronic pain conditions that afflict the elderly 5 4 3 2 1
- Describe clinical strategies that incorporate the recently published guidelines and the principles of rational polypharmacy to design a treatment approach that provides efficacy and minimizes side effects 5 4 3 2 1

Overall Effectiveness of the Activity

- Was timely and will influence how I practice 5 4 3 2 1
- Will assist me in improving patient care 5 4 3 2 1
- Fulfilled my educational needs 5 4 3 2 1
- Avoided commercial bias or influence 5 4 3 2 1

Impact of the Activity

The information presented:

(check all that apply)

- Reinforced my current practice/treatment habits Will improve my practice/patient outcomes
- Provided new ideas or information I expect to use Enhanced my current knowledge base

Will the information presented cause you to make any changes in your practice? Yes No

If yes, please describe any change(s) you plan to make in your practice as a result of this conference:

How committed are you to making these changes?

5 (Very committed) 4 3 2 1 (Not at all committed)

Future Activities

Do you feel future activities on this subject matter are necessary and/or important to your practice? Yes No

Please list any other topics that would be of interest to you for future educational activities:

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would like to participate in such a survey:

- Yes, I would be interested in participating in a follow-up survey. No, I'm not interested in participating in a follow-up survey.

Additional comments about this activity:

If you wish to receive acknowledgment of participation for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Post-test Answer Key

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|----|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| | | | | | | | | | |

Request for Credit

Name _____ Degree _____

Organization _____ Specialty _____

Address _____

City, State, ZIP Code _____

Telephone _____ Fax _____ E-mail _____

Signature _____ Date Completed _____

For Physicians Only

I certify my actual time spent to complete this educational activity to be: _____

- I participated in the entire activity and claim 1.0 credit. I participated in only part of the activity and claim _____ credit.

