EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants should be able to:
• Describe the proposed pathophysiologic mechanisms for chronic nociceptive and neuropathic pain.
• Understand the evidence from recent clinical trials and experience using systemic and topical analgesics for the treatment of common chronic pain disorders.
• Assess the strengths and limitations of current pharmacologic treatment strategies for the management of chronic nociceptive and neuropathic pain in the elderly.
• Discuss approaches to minimize the risk of adverse side effects and drug interactions in the elderly patient.
Pharmacologic Treatment of Chronic Pain in the Elderly

Program Release Date: June 2004
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About the Program
This activity on pharmacologic treatment of chronic pain in the elderly has been developed and approved by the authors listed under the direction of the Office of Continuing Professional Education at the University of Rochester School of Medicine and Dentistry. It addresses an identified educational need for information on the pharmacologic treatment of chronic pain in elderly patients.

Target Audience
This activity is intended for clinicians who diagnose and treat chronic pain in the elderly, including geriatricians, internists, family physicians, general practitioners, long-term care medical directors, consultant pharmacists, and nurse practitioners.

Educational Objectives
Upon completion of this activity, participants should be able to:
• Describe the proposed pathophysiologic mechanisms for chronic nociceptive and neuropathic pain.
• Recognize the evidence from recent clinical trials and experience using systemic and topical analgesics for the treatment of common chronic pain disorders.
• Assess the strengths and limitations of current pharmacologic treatment strategies for the management of chronic nociceptive and neuropathic pain in the elderly.
• Discuss approaches to minimize the risk of adverse side effects and drug interactions in the elderly patient.

Certification
The University of Rochester School of Medicine and Dentistry designates this educational activity for a maximum of 1 Category 1 credit toward the AMA Physician’s Recognition Award. Each physician should claim only those credits that he/she actually spent in the educational activity.

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Dr. Robert Dworkin reported that he has received research support, consulting fees, or speakers’ bureau honoraria in the past year from Allergan Inc., Alpharma Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Inc., Eli Lilly and Company, Endo Pharmaceuticals, Epilepsy Corporation, GlaxoSmithKline, Johnson & Johnson, Merck KgaA, NeurogesX, Inc., Novartis Pharmaceuticals, Pfizer Inc, Purdue Pharma LP, and Reliant Pharmaceuticals, Inc. He has discussed unapproved or off-label use of products in this presentation.

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The growing population of elderly persons in the United States has spawned the development of professional societies, medical subspecialties, and governmental institutions aimed at promoting health and well-being as well as scientifically exploring the aging process.1–3 Pain is common in the elderly, particularly in those over the age of 75 years. The incidence of pain rises from 34% in people aged 75–79 to 50% in those over 90 years old. The incidence of severe pain also increases with age, from 15% in those 75–79 years old to 28% in individuals over 90 years old.

Persistent pain is associated with depression and anxiety and other psychosocial comorbidities, impaired ability to perform activities of daily living and engage in social activities, and increased health care utilization and costs.1 Because of functional limitations and the overall lower quality of life in individuals with pain, the inadequate management of pain in the elderly can have very broad personal, health care, and societal consequences.

An Overview of Pain

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”4 Pain is therefore a subjective experience that is assessed by means of the patient’s report of its presence and its intensity. There are many different types of pain, and one important distinction is between acute and chronic pain. Acute pain refers to conditions such as postoperative pain or short-lived pain associated with various diseases (eg, herpes zoster) and injuries (eg, limb fracture). It is a common experience, easier to diagnose than persistent pain, and with treatments that are generally effective and a course that is well-defined and usually relatively short.

Although clearly related to acute pain, chronic pain has become accepted as a distinct phenomenon that can be defined as pain that persists beyond the normal time of healing, which can generally be considered 3 months.4 With chronic pain, there is typically no effective therapy for the underlying disease process and a much more complex interaction between the physiologic input and the emotional processes that shape an individual’s perception and response to that input.

A second major distinction is based on the presumed etiology of the pain, namely nociceptive pain versus neuropathic pain. Nociceptive pain refers to pain that is associated with tissue damage and that is mediated by an intact nervous system; it is often described as throbbing or aching. Neuropathic pain is caused by injury or dysfunction of the peripheral and/or central nervous system, and it is often described as burning or shooting, with other qualities that the patient finds unfamiliar. It can be very difficult to be certain of the exact type of pain a patient is experiencing. Many chronically ill patients have a pain syndrome with both somatic and neuropathic components. As will be seen below, low back pain that is chronic, nonmalignant, and non-neuropathic would be treated quite differently from back pain that results from metastatic disease compressing nervous system tissue.

Assessment of Pain in the Elderly

The assessment of pain begins with an evaluation of the location, quality, duration, and timing of the pain, as well as its provocative and ameliorating factors. A variety of scales are available that have been validated in the elderly.1,3,5 Many older patients can describe the severity of their pain with a 0–10 scale, with 0 indicating “no pain” and 10 indicating “worst possible pain.” However, pain assessment can be particularly challenging in this population,1,3 and confounding neuropsychiatric conditions such as memory loss, dementia, and depression can make assessment problematic.6 Also, the elderly tend to under-report their pain symptoms for various reasons. First, for many patients, admitting that pain exists reflects advancing disease and subsequent approaching death, a logical reason for denial.5 Second, many elderly patients believe that their physicians already know about their pain and are appropriately treating it.5 Third, most elderly patients feel that pain is a natural part of aging. Although cognitive impairment may be a substantial barrier to pain assessment, recent studies have suggested that impaired patients can respond to pain questionnaires if they are presented in a manner sensitive to their function (eg, visual cues with large print).6,7

Physiologic Changes and Drug Interactions in the Elderly

The physiologic changes associated with aging alter the pharmacokinetics of many drugs including analgesic medications. This predisposes the elderly to an increased risk of adverse effects. Conditions that are associated with aging may induce changes in drug absorption, elimination, metabolism, and distribution.8 Age-related changes in body mass composition lead to changes in the volume of distribution of drugs. For example, the volume of distribution decreases for hydrophilic drugs and increases for lipophilic drugs. Thus, a bolus dose of a hydrophilic drug (eg, morphine) can cause a greater clinical effect when comparing the elderly to younger patients. Age-related decreases in available sites for protein-binding of drugs occur secondary to a decline in albumin and plasma proteins, secondary to poor nutrition or chronic disease states. The higher proportion of unbound drug effectively increases the potency for a given dose of medication. Age-related declines in hepatic and renal function lead to higher drug concentrations, as well as reduced drug metabolism and excretion.2 The common practice of polypharmacy in elderly persons with many health conditions leads to an increased risk of both pharmacokinetic and pharmacodynamic drug interactions.3 In one study of 332 nursing home residents studied over a 4-year period, 67% of the residents experienced one or more adverse drug reactions, which were most commonly cardiovascular, central nervous system, and gastrointestinal.9 Appropriate pain therapy must attempt to minimize the risks of adverse drug reactions.
Chronic Nociceptive Pain

Nociceptive pain is transmitted to the nervous system through activation of specific tissue receptors called nociceptors. Subtypes of nociceptors include receptors sensitive to mechanical, thermal, or chemical stimuli. In fact, some types of nociceptors respond to more than one stimulus. Examples of nociceptive pain conditions include fractures, burns, osteoarthritis, and musculoskeletal low back pain. Nociceptive pain commonly responds to conventional analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics, and it may also respond to various nonpharmacologic therapies.

The predominant causes of pain in the elderly appear to be musculoskeletal. The most common form of musculoskeletal pain is osteoarthritis, afflicting over 20 million Americans each year. The incidence of osteoarthritis, increases with age and an incidence of 52 of 1000 patients 18-44 years of age and increasing to 508 of 1000 persons older than 75 years of age. Out of 697 of 864 people over the age of 65 who were screened for osteoarthritis, 30% suffered from osteoarthritis of the knee, 15% had arthritis of the hip, and 8% had arthritis of the hand. Osteoarthritis affects approximately 80% of patients older than 65, and most of this pain is clinically significant. There is no cure available for osteoarthritis, and direct and indirect costs of therapy and lost productivity reach billions of dollars annually. The aim of current therapy is appropriate pain management and improved quality of life while minimizing toxicity from the drugs prescribed.

Since the elderly are more likely to suffer from a malignant condition, cancer-related pain is a common source of pain in this population. Cancer-related pain, which may be nociceptive, neuropathic, or both, arises from tumor burden or recurrence, cancer, infection, and inflammatory arthritis. Non-mechanical pain occurs in older adults with higher prevalence and malignancy and can be the cause of low back pain in up to 7% of patients over age 50. Mechanical low back pain may be caused by sprains, strains, myofascial pain, fibromyalgia, facet and disc disease, osteoporotic compression fracture, and spondylolisthesis.

Pharmacologic Strategies for Management of Nociceptive Pain

Pharmacotherapy, the most common form of treatment for pain in elderly patients, requires careful consideration of the patient's comorbid conditions and concurrent medications, as well as a full review of the pharmacokinetic and pharmacodynamic profiles of medications. Drugs that can be used for nociceptive pain include acetaminophen, NSAIDs, including cyclooxygenase (COX)-2 agents, opioid analgesics, and topical medications. Each class of medication carries its own profile of risks and benefits in the elderly.

Acetaminophen is the analgesic that is recommended by both the American College of Rheumatology and the American Geriatrics Society for the initial treatment of osteoarthritis. The American Pain Society, in the most recent review of the treatment of osteoarthritis, limits the use of acetaminophen for only mild pain with the specific COX inhibitors being advised for moderate-to-severe pain. Two studies have demonstrated analgesic equivalence of acetaminophen when compared to ibuprofen and naproxen. A few studies have suggested that the analgesic efficacy achieved by rofecoxib and diclofenac may be superior to acetaminophen (paracetamol) in the routine treatment of osteoarthritis. The routine recommendation for using acetaminophen in the management of osteoarthritis is due to the lower incidence of gastric bleeds and lower costs when compared to the traditional NSAIDs. A recent epidemiologic study has demonstrated that higher dosages of acetaminophen may be associated with gastrointestinal bleeding, although this remains a rare event in clinical practice. Prospective double-blind randomized trials have not been completed to determine the gastrointestinal risk of acetaminophen. Acetaminophen is commonly used for the management of breakthrough pain to supplement NSAIDs. An acute pain study, however, demonstrated that the addition of 2 grams of acetaminophen did not improve the analgesia achieved with rofecoxib 50 mg.

NSAIDs remain a first-line therapy for osteoarthritis, low back pain, and other nociceptive pain conditions in the elderly, although their chronic use in older adults must be monitored very closely. Choices for NSAID therapy now include both the traditional nonspecific COX inhibitors (eg, ibuprofen, piroxicam, naproxen) and the specific COX-2 inhibitors (eg, valdecoxib, rofecoxib, celecoxib). There are idiosyncratic differences in how patients respond to the traditional NSAIDs with controlled studies showing minimal differences between the agents. As analgesics, the newer COX-2 inhibitors are as effective as the traditional NSAIDs, but with a reduced risk of gastric bleeds. In an epidemiologic study in patients older than 65 years of age in Ontario, Canada, the risk of gastrointestinal bleeding was four times greater with traditional NSAIDs than in the control group, but with celecoxib was similar to the control group. The use of misoprostol combined with diclofenac reduced the risk of bleeding to three times less than controls. An update to criteria for potentially inappropriate medication use in the elderly listed a number of traditional nonspecific NSAIDs that should not be used in the elderly. These guidelines advise against the use of indomethacin and ketorolac in this population. In addition, the risks of gastric bleeds and hypertension are considered unacceptable for NSAIDs that have long elimination half-lives, such as naproxen, piroxicam, and oxaprozin.

Numerous recent studies have documented the efficacy of NSAIDs in the arthritides. Clemett et al showed that celecoxib at dosages of 100-200 mg increased functional status for a 2-week period when compared to placebo. Chavez and DeKorte reviewed 14 studies of valdecoxib including more than 4000 patients. An injectable form of this drug is under study, and once approved is anticipated to be useful in the elderly with severe pain. Two studies have demonstrated analgesic equivalence of acetaminophen when compared to ibuprofen and naproxen. Traditional NSAIDs have often been added to cardiovascular-protective
Meperidine and propoxyphene have active toxic metabolites that equipotent dose may be too large. The key to titrating long-acting methadone from other opioids. Patients who are taking high doses care. Particular caution should be applied when converting to long and variable half-life, its administration requires additional effective drug for pain management in the elderly, but due to its These include transcutaneous fentanyl, long-acting morphine, and morphine is usually the first-line drug. However, in the elderly, toxic metabolites can build up (especially morphine-6-glucuronide). This is especially true in those patients with renal impairment. Long-acting formulations of opioids are effective in the elderly but require a great deal of care when titrating to the steady state. These include transcutaneous fentanyl, long-acting morphine, and long-acting oxycodone preparations. Methadone can be a very effective drug for pain management in the elderly, but due to its long and variable half-life, its administration requires additional care. Particular caution should be applied when converting to methadone from other opioids. Patients who are taking high doses of morphine, oxycodone, or hydromorphone for chronic pain may show unexpected sensitivity to methadone so that the calculated equipotent dose may be too large. The key to titrating long-acting opioids is to advance the dosage very slowly over weeks, while using adequate doses of short-acting medication for breakthrough pain. Meperidine and propoxyphene have active toxic metabolites that can rapidly build up in the elderly, so their use is discouraged.

Griesinger et al suggests that several general principles should be followed when prescribing opioids for elderly patients. It is essential to use a low initial dose with slow titration and prolonged dosage intervals. Laxatives and stool softeners should be given simultaneously, as constipation rates can approach 100%. Finally, monitoring of renal function should be performed. Adhering to these suggestions greatly improves compliance and overall efficacy of opioid analgesics in the elderly. A recent review by Kurz and Sessler describes the mechanism of opioid-induced bowel dysfunction and discusses two drugs still in clinical trials, methylaltrexone and alvimopan. Both drugs antagonize opioid action in the gut and may not be absorbed in sufficient quantity to result in pain due to opioid antagonism at the analgesic sites of action in the brain and spinal cord.

A meta-analysis of topical NSAIDs in the treatment of osteoarthritis demonstrated that in 7 of 12 studies, topical NSAIDs were superior to placebo, but no study showed any benefit when compared to oral NSAIDs. A newer medication is the lidocaine patch 5%, which is a 10- x 14-cm nonwoven felt patch that contains 700 mg of aqueous-based lidocaine in the adhesive. Although 700 mg represents a toxic injected lidocaine dose, absorption through the skin is limited and produces very low serum levels. Its lack of drug–drug interactions and very low incidence of serious systemic side effects make it an ideal agent in older patients. The lidocaine patch has been approved by the FDA for the treatment of postherpetic neuralgia with an indicat-ed dosage of up to three patches on for 12 hours then off for 12 hours (see below). Ongoing evaluations are examining the drug’s effectiveness in nociceptive pain states, such as low back pain and osteoarthritis. Case reports suggested that the lidocaine patch may have value in the treatment of chronic low back pain, and recent prospective open-label studies assessed the value of four patches in the treatment of 131 low back pain patients and 137 patients with painful osteoarthritis. The lidocaine patch provided significant improvement in pain intensity and pain relief as well as in various measures of quality of life and depression.

Low back pain also responds to procedural intervention, particularly when the etiology is clear. Facet and disc disease as well as spinal stenosis may respond to injections of depocorticosteroid. Epidural steroid injection is widely available and has been shown to shorten the duration of painful sciatic symptoms due to disc herniation, although it has no effect on the incidence of surgery. The mechanism of injury should be sought and instruction in biomechanics offered if a preventable etiology is identified. More sophisticated procedural interventions are also available including radiofrequency neuroablative, vertebroplasty, and the use of spinal cord and motor cortex stimulation. Analgesic infusion into the epidural and intrathecal space is discussed below. When low back pain has a neuropathic component, a sodium channel–active drug such as gabapentin or a tricyclic drug like nortriptyline may be helpful.

Cancer Pain

Cancer currently affects an estimated 1.4 million new patients and causes 560,000 deaths annually. The elderly are at an increased risk for undertreatment of cancer pain. In the U.S., over 50% of cancers occur in individuals aged 65 and older. End-of-life considerations and palliative care become extremely important for cancer pain patients with advanced disease.

Patients with advanced disease usually have more than one source of their pain. According to Twycross et al, the vast majority of pain in patients with cancer originates from increasing tumor growth. Ironically, many cancer therapies, such as chemotherapeutic agents and radiation therapy, are also potential sources of cancer pain in the elderly.

Cancer, like nonmalignant pain, can be divided into nociceptive and neuropathic types. Nociceptive bone and soft tissue pain are commonly due to tumor invasion. Direct chemotherapeutic effects (eg, abdominal pain, oral mucositis) are other common causes of cancer-related nociceptive pain. Neuropathic pain may also develop with neurotoxic chemotherapeutic agents as well as with neuropathy from tumor burden (nerve entrapment syndromes).

Strategies available to manage most cancer pain have been formally introduced by the World Health Organization. They include a stepwise approach utilizing conventional analgesics as well as weak and potent opioids. Opioid-related side effects can be a problem in the cancer pain population. Many patients require large dosages of long-acting opioid medication to obtain adequate pain relief. Opioid rotation is a common method used for decreasing side effects. This strategy works because there is large individual variation in the pattern of adverse effects produced by different opioids. Equipotent analgesic tables can serve as a rough guide for rotation. However, equipotent tables are not reliable when switching from another opi-
oid to methadone, and consultation with a physician experienced in these conversions is suggested.

Neural blockade, neurolysis, and implantable drug delivery systems should be considered in elderly cancer patients who have unremitting pain despite pharmacotherapy. For example, neurolytic celiac plexus blockade is an option in patients with pancreatic carcinoma who have intractable pain and are poorly responsive to systemic medications. The reliable 3 months of symptom relief may provide lifelong pain relief. Neuraxial opioid administration by epidural or intrathecal route is an effective option in elderly patients with cancer pain who have a partial response to systemic opioids but suffer intolerable side effects, which limit the dose that can be administered.

When spinal nerve is invaded by cancerous growth, a multimodal approach should be sought. Opioid and nonopioid medications should be titrated to bring pain under control until chemotherapy, radiotherapy, or surgery can relieve the compression. Side effects such as sedation and constipation should be aggressively treated. Modafinil or methylphenidate may be helpful in treating sedation, while stool softeners and soon to be released naloxone-like opioid antagonists that remain in the gut will be helpful for constipation.

**Chronic Neuropathic Pain**

Neuropathic pain can result from damage to nerve fibers themselves or to central nervous system pain control mechanisms. Important signs and symptoms commonly found in patients with neuropathic pain include allodynia (pain arising from a nonpainful stimulus), hyperalgesia (an exaggerated response to a painful stimulus), paresthesias (abnormal sensations, such as tingling), and dysesthesias (abnormal sensations that are unpleasant). Patients with neuropathic pain usually manifest additional evidence of neurologic dysfunction in the form of weakness or sensory loss in an appropriate pattern for the level of nervous system dysfunction.

Neuropathic pain syndromes that are common in older individuals include postherpetic neuralgia (PHN), painful diabetic neuropathy (PDN), and central post-stroke pain. PHN is diagnosed when the pain associated with herpes zoster ("shingles") does not resolve, which occurs in a substantial number of patients. Herpes zoster is caused by the reactivation of the varicella-zoster virus and its spread from a single sensory ganglion to the corresponding dermatome and neural tissue of the same segment, typically decades following a primary chickenpox infection. Importantly, older age is not only a risk factor for herpes zoster but is also a very well-established risk factor for identifying which patients with zoster have an increased likelihood of developing PHN. Other risk factors for PHN include more severe acute pain during zoster, more severe rash, and history of a prodrome of pain in the affected dermatome before the rash appears. Long-term care patients are at increased risk for both herpes zoster and PHN because both of these conditions are more prevalent in the elderly and because herpes zoster is also associated with immunosuppression from several diseases or medications.

Over 14 million adults in the United States have diabetes mellitus, and diabetic neuropathy is one of its most common complications, occurring in approximately 50% of patients who have had diabetes for 25 years. A recent review concluded that as many as 20-24% of patients with diabetes may have PDN. In patients with diabetes, increased age, greater duration of diabetes, and poorer glycemic control are risk factors for diabetic neuropathy, and these factors also appear likely to increase the risk of developing a painful neuropathy. Studies have found that maintaining proper glucose control slows and may even prevent the progression of diabetic neuropathy.

The symptoms of PDN usually start bilaterally in the toes and feet and may, in some patients, gradually spread to involve the calves and knees (ie, a "stocking" pattern). If symptoms progress to the upper calf or knee, patients may also begin to notice symptoms of pain or abnormal sensations not only in their lower limbs, but also in their fingers and hands (ie, a "stocking-and-glove" pattern). Most patients report a worsening of pain during the night, and in some, pain is only prominent at bedtime. Bilateral burning foot pain is common in diabetic neuropathy, but burning feet can also occur in older patients in association with impaired glucose tolerance (which can be identified with a 2-hour glucose tolerance test), hypertriglyceridemia, Sjögren’s syndrome, and B12 deficiency, and can often be the predominant symptom of an idiopathic sensory polyneuropathy.

Central neuropathic pain has been described following cerebral infarction of multiple brain regions, including lesions in the thalamus, brainstem, and cortex. The pain region depends on the brain structure affected and can involve an entire hemibody region or only a small body region, such as within a limb. The pain is typically located in the region of other neurologic deficits. Central post-stroke pain has also been termed the thalamic pain syndrome and was originally named Dejerine-Roussy syndrome for the physicians who first described this condition in 1906.

**Mechanisms of Neuropathic Pain**

There have been a large number of studies of pain mechanisms using animal models of neuropathic pain. One implication of the results of these studies has been the recognition that pain syndromes identified by disease (eg, PHN or PDN) most likely have multiple distinct mechanisms that account for chronic pain and are reflected in different patterns of symptoms and signs. Hence, a neuropathic pain syndrome can include heterogeneous groups of patients that differ in their mechanisms and symptoms, and, as a consequence, in their treatment response and prognosis.

One of the best examples of the mechanism-based approach to neuropathic pain is the proposal by Rowbotham et al and Fields et al that there are separate mechanisms involved in PHN and that these mechanisms are reflected in different subtypes of patients. In their studies, patients with PHN and prominent allodynia were found to have relatively normal sensory function as assessed by thermal thresholds, and were also more likely to report pain relief following local anesthetic infiltration with lidocaine than patients with primarily constant pain. It was concluded that the mechanism of PHN in patients with allodynia is abnormal activity in primary afferent nociceptors that have been damaged by the varicella-zoster virus; this abnormal activity initiates and then maintains a state of central sensitization in which input from large fiber afferents that respond to nonpainful mechanical stimuli cause allodynia. Patients with PHN with predominantly continuous pain were found to have sensory loss in the areas where they have the most pain. This suggests that continuous pain in PHN is caused by a different mechanism than allodynia, possibly involving central structural and functional changes accompanying deafferentation.
Guidelines for the treatment of neuropathic pain have recently been published that were based on the results of randomized controlled trials and the clinical experience of a group of neuropathic pain clinicians and researchers. It is important to acknowledge before discussing these recommendations that the United States Food and Drug Administration has approved medications for the treatment of only two specific neuropathic pain syndromes: carbamazepine in trigeminal neuralgia, and gabapentin and lidocaine patch 5% in PHN. The applicability of the results of clinical trials in one chronic neuropathic syndrome to other chronic neuropathic syndromes is unknown, but most of the first-line therapies identified in the guidelines have been tested in several types of neuropathic pain with generally similar results.

First-Line Medications. Although many different medications have been used in the treatment of neuropathic pain, until recently only tricyclic antidepressants (TCAs) had been evaluated in multiple randomized, double-blind, placebo-controlled clinical trials. However, the efficacy of each of five pharmacologic treatments in patients with neuropathic pain has now been demonstrated by the results of multiple, consistent randomized controlled trials. These five medications—gabapentin, lidocaine patch 5%, opioid analgesics, tramadol, and TCAs—provide the clinician with an evidence-based approach for the first-line treatment of neuropathic pain. There are clinical circumstances in which each one can be used in the initial treatment of patients with neuropathic pain. Opioid analgesics and TCAs, however, are treatments that generally require greater caution and have poorer tolerability and less overall ease of use, and the initiation of treatment with these drugs can therefore be expected to occur less frequently. The Table presents an overview of these treatment guidelines for neuropathic pain.

There are nine published, double-blind, placebo-controlled, randomized clinical trials of gabapentin in patients with PHN, PDN, mixed neuropathic pain syndromes, phantom limb pain, Guillain-Barré syndrome, and acute and chronic spinal cord injury pain. Gabapentin at daily dosages up to 3600 mg significantly reduced pain compared to placebo, and improvements in sleep, mood, and quality of life were also demonstrated in some trials. The side effects of gabapentin include somnolence and dizziness, and less often, gastrointestinal symptoms and mild peripheral edema, all of which require monitoring and dose adjustment but usually not drug discontinuation. Gabapentin may cause or exacerbate gait and balance problems and cognitive impairment in the elderly, and dosage adjustment is necessary in patients with renal insufficiency. However, its generally excellent tolerability, safety, and lack of drug interactions distinguish gabapentin from most other oral medications used in the treatment of chronic neuropathic pain.

There are three published, double-blind, vehicle-controlled, randomized clinical trials of lidocaine patch 5% that demonstrated statistically significantly greater pain relief with the lidocaine patch compared with vehicle-control patches; two of these studies were conducted in patients with PHN and one in a group of patients with diverse peripheral neuropathic pain syndromes, half of whom had PHN. The lidocaine patch is a topical preparation, and in patients with normal hepatic function, blood levels are minimal and accumulation does not occur with the 12-hour-on, 12-hour-off dosing schedule. Lidocaine patch 5% has excellent safety and tolerability, and the only side effects involve mild skin reactions (eg, erythema, rash).

### TABLE

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

Systemic absorption from lidocaine patch 5% must be considered in patients receiving oral class I antiarrhythmic drugs (eg, mexiletine).

Seven double-blind, randomized trials of oral opioid analgesics have been published since 1998 in patients with PHN, PDN, phantom limb pain, and a variety of peripheral and central neuropathic pain syndromes. The results of these seven studies considered together provide the basis for considering opioid analgesics a first-line treatment for neuropathic pain. The most common side effects of opioid analgesics are constipation, sedation, and nausea. In elderly patients treated with opioid analgesics, cognitive impairment and problems with mobility can occur. Opioid analgesics must be used very cautiously in patients with a history of substance abuse or suicide, and accidental death or suicide can occur with overdose. Patients treated with opioid analgesics may develop analgesic tolerance (ie, a reduction in analgesic benefit over time), although a stable dosage can usually be achieved. All patients treated with opioids will develop physical dependence (ie, withdrawal symptoms develop with abrupt discontinuation or rapid dose reduction), and they must be advised not to abruptly discontinue the medication.

There are three published, double-blind, placebo-controlled, randomized clinical trials of tramadol in neuropathic pain, one in patients with PDN, one in patients with painful polyneuropathy of different etiologies including PDN, and one in patients with PHN. In these trials, tramadol titrated to a maximum dosage of 400 mg daily significantly relieved pain compared to placebo, and beneficial effects of treatment on allodynia and quality of life were also reported. The side effects of tramadol include dizziness, nausea, constipation, somnolence, and orthostatic hypotension, which occur more frequently when the dosage is escalated rapidly. There is an increased risk of seizures in patients treated with tramadol who have a history of seizures or who are also receiving antidepressants, opioids, or other drugs that can reduce the seizure threshold. Serotonin syndrome may occur if tramadol is used concurrently with other serotonergic medications. Tramadol may cause or exacerbate cognitive impairment in the elderly, and dosage adjustment is necessary in patients with renal or hepatic disease. Abuse of tramadol is thought to be rare but has been observed.

Tricyclic antidepressant drugs were the first type of medication proven effective for neuropathic pain in placebo-controlled trials. Although clinical trials of patients with HIV sensory neuropathy, spinal cord injury pain, and cis-platinum neuropathy found little benefit of amitriptyline when compared with placebo, an apt summary of the overall efficacy of TCAs in neuropathic pain was provided by Mitchell Max in the title of a review of their efficacy. "Thirteen Consecutive Well-Designed Randomized Trials Show That Antidepressants Reduce Pain in Diabetic Neuropathy and Postherpetic Neuralgia." TCAs must be used very cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention, and autonomic neuropathy. Almost 20% of patients treated with a tricyclic antidepressant after a myocardial infarction developed adverse cardiac events in a recent study. and a screening electrocardiogram to check for cardiac conduction abnormalities is recommended before beginning treatment with TCAs, especially in patients over 40 years of age. As with opioid analgesics, TCAs must be used cautiously when there is a risk of suicide or accidental death from overdose. TCAs may block the effects of certain antihypertensive drugs and they interact with drugs metabolized by P-450 2D6. All selective serotonin reuptake inhibitors (SSRIs) inhibit P-450 2D6, and caution must be exercised in the concomitant administration of TCAs and SSRIs and in switching from one drug class to the other. In the elderly, TCAs may cause balance problems and cognitive impairment. Milder side effects of TCAs include sedation, anticholinergic effects, postural hypotension, and weight gain.

Most clinical trials of TCAs in neuropathic pain have examined amitriptyline, but amitriptyline is not recommended in elderly patients because of the risk of significant adverse events. Nortriptyline and desipramine have fewer side effects and are generally better tolerated than amitriptyline. In a recent randomized double-blind trial, nortriptyline was found to provide equivalent analgesic benefits in patients with PHN when directly compared with amitriptyline but was better tolerated. Regardless of which TCA is used, patients must be informed that TCAs have an analgesic effect that has been demonstrated to be independent of their antidepressant effect.

**Sequential and Combination Treatment With First-Line Medications.** As discussed above, current understanding of the pathophysiology of neuropathic pain is consistent with the existence of multiple pain mechanisms, which may each respond differently to medications with different mechanisms of action. It can therefore be recommended that patients who do not respond to one of these five first-line medications be treated with one or more of the others. Despite the lack of controlled data, the use of combinations of two or more of these first-line medications can be recommended when patients have a partial response to a single one, and also at the beginning of treatment either to increase the likelihood of a beneficial response or when a medication that requires titration to reach an effective dosage is also being used. Disadvantages of combination therapy include an increased risk of side effects as the number of medications is increased. It is also important to emphasize that the medications that are currently available are rarely associated with the complete relief of neuropathic pain, and evidence of their beneficial effects on quality of life is limited. Because medical management of the patient with neuropathic pain rarely provides a cure, it should be considered an integral component of a more comprehensive approach to treatment, which may include various nonpharmacologic treatments such as psychological counseling, physical therapy, and alternative and complementary medicine approaches such as acupuncture.

**Conclusions**

The elderly present a unique set of challenges when attempting to assess and treat pain. Fortunately, health care professionals are becoming more aware of potential pharmacologic and nonpharmacologic strategies for pain reduction in this population. Development of new treatments for pain is continuing at a rapid pace, and progress in basic neuroscience and in identifying the psychological aspects of pain will lead to a greater understanding of the underlying mechanisms of chronic pain. These advances will make it possible to go beyond the determination of whether treatment is efficacious to the identification of what treatments are most effective for which patients.
References

CME Examination & Evaluation
Pharmacologic Treatment of Chronic Pain in the Elderly

To obtain continuing medical education credit, please (1) circle your responses on the following CME Examination, (2) complete the Participant Information, (3) fill out the CME Evaluation, and (4) fax or mail this page to:

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CME Examination
(Please circle the correct answer.)

1. Low back pain is responsible for 3% of office visits and presents in up to 20% of adults over 65.
   a. True  b. False
2. Which of the following can be a cause of mechanical low back pain in older patients?
   a. Myofascial pain
   b. Fibromyalgia
   c. Facet syndrome
   d. All of the above
3. Based on at least one report, malignancy is the cause of low back pain in more than 5% of patients over age 50.
   a. True  b. False
4. Which of the following is TRUE regarding epidural injection of depocorticosteroid?
   a. Speeds healing of ruptured disc
   b. Decreases incidence of surgical intervention
   c. Duration of painful symptoms is shortened
   d. All of the above
5. When cancer pain responds poorly to parenteral and enteral analgesic medication, which of the following interventions should be considered?
   a. Celiac plexus blockade/neuroablation for pancreatic cancer
   b. Increase the efficacy of opioid medication and decrease the side-effect profile by spinal or epidural catheter infusion
c. Treat side effects to increase the dose of opioid that can be tolerated
d. All of the above
6. Which of the following are risk factors for the development of postherpetic neuralgia following a herpes zoster infection?
   a. Older age
   b. Severe acute pain during the infection
c. Male sex
d. Both a and b
e. Both a and c
7. Allodynia, which is common in patients with neuropathic pain, is best described as:
   a. Paroxysmal pain in a dermatomal distribution
   b. Stimulus-evoked pain in response to normally non-painful stimuli
c. Continuous burning pain
d. Increased pain in response to a normally painful stimulus
e. None of the above
8. Which of the following processes are thought to play a role in the pathophysiology of neuropathic pain?
   a. Activity in damaged nociceptors
   b. Central sensitization in the dorsal horn of the spinal cord
c. Continuous burning pain
d. Both a and b
e. Both a and c
9. Pharmacologic agents that have demonstrated efficacy in randomized clinical trials in patients with neuropathic pain include:
   a. Tricyclic antidepressants
   b. Topical lidocaine patch
   c. Gabapentin
d. Opioid analgesics
e. All of the above
10. Which of the following antidepressants has the optimal profile of analgesic effect and tolerability for patients with neuropathic pain?
    a. Amitriptyline
    b. Mirtazapine
    c. Nortriptyline
d. Fluoxetine
e. Doxepin

Participant Information
(Please print.)

Name: ____________________________________________ Degree: ____________________________
Title: ____________________________________________ Specialty: ____________________________
Institution: ________________________________________
Street: ______________________________________________________________________________
City: ____________________________ State: ___________ Zip code: ____________________________
Telephone: ____________________________ E-mail: ____________________________________________
Signature: ____________________________________________________________________________

I certify that I have completed this activity as designed.

CME Evaluation
Please circle the number that best reflects your opinions on the following statements, using the following rating scale:
1 = Strongly Agree; 2 = Agree; 3 = Disagree; 4 = Strongly Disagree.

1. After this activity, I am better able to:
   • Describe the proposed pathophysiologic mechanisms for chronic nociceptive and neuropathic pain.
   • Recognize the evidence from recent clinical trials and experience using topical and systemic analgesics for the treatment of common chronic pain disorders.
   • Assess the strengths and limitations of current pharmacologic treatment strategies for the management of chronic nociceptive and neuropathic pain in the elderly.
   • Discuss approaches to minimize the risk of adverse side effects and drug interactions in the elderly patient.
   1 2 3 4
2. This activity was presented in a clear and organized manner.
   1 2 3 4
3. The content was scientific, objective, fair-balanced, and independent from commercial bias.
   1 2 3 4
4. As a result of this learning experience, I hope to make the following changes in my current clinical practice:
   ____________
5. I plan to retain this supplement for my personal library: ___ Yes ___ No

Within 4 weeks of sending in these materials (CME Examination, Participant Information, and CME Evaluation), you will receive a CME certificate and an annotated answer sheet if you successfully completed the examination. There is no charge to the learner to apply for CME credit. Please phone (585) 275-4392 with any questions.