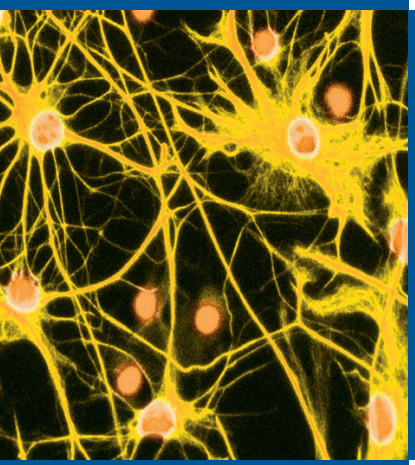

Breakthroughs and Challenges in the Management of Common Chronic Pain Conditions: A Focus on Neuropathic Pain

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STATEMENT OF NEED

As many as 50 million people will experience chronic pain at some point in their lives. However, chronic pain is often not viewed as a medical condition that warrants treatment.[1] In a survey by the American Pain Society (APS), while more than 9 out of 10 people with moderate to severe chronic pain reported seeking medical care for pain management, almost half reported changing clinicians at least once for several reasons. Either the pain persisted (42%), or the clinician was not knowledgeable about pain (31%), did not take the patient's pain seriously (29%), or was unwilling to provide aggressive treatment (27%).[2] Primary care clinicians treat numerous medical conditions that may result in chronic neuropathic pain, including painful diabetic neuropathy (PDN), postherpetic neuralgia (PHN), and chronic low back pain.[3] The information provided in this publication will assist clinicians in understanding the major mechanisms involved in chronic pain, as well as the current research and consensus on the most effective pharmacologic approaches for chronic pain management.

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BREAKTHROUGHS AND CHALLENGES IN THE MANAGEMENT OF COMMON CHRONIC PAIN CONDITIONS: A FOCUS ON NEUROPATHIC PAIN

Introduction

Chronic pain partially or totally disables as many as 50 million people during their lifetime, yet is often not viewed as a medical condition that warrants treatment.[1] A survey conducted by the American Pain Society (APS) showed that while 94% of people with moderate to severe chronic pain sought medical care for pain management, almost half (47%) changed clinicians at least once—because the pain persisted (42%); the clinician was not knowledgeable about pain (31%); the clinician did not take the patient's pain seriously (29%); or the clinician was unwilling to provide aggressive treatment (27%).[2] Since the ongoing care of patients with chronic pain often is provided by primary care clinicians, clinicians need to understand the major mechanisms involved in chronic pain, as well as effective pharmacologic approaches for chronic pain management.

Primary care clinicians treat numerous medical conditions that may result in chronic neuropathic pain, including painful peripheral neuropathy in patients with diabetes (PDN), and postherpetic neuralgia (PHN) as a sequelae of shingles. These 2 neuropathic pain problems affect over a million patients. Other common neuropathic pain conditions are listed in Table 1, including neuropathic low back pain, which afflicts over 2 million patients.

The Physiology of Acute Pain

Acute pain follows tissue injury and has the physiologic function of protecting the organism from further injury. Acute pain diminishes with healing, and disappears when healing is complete.

TARGET AUDIENCE

Neurologists, primary care clinicians, nurse practitioners, and other healthcare professionals who treat patients with chronic pain.

EDUCATIONAL OBJECTIVES

After completing this publication, participants should be able to:

- Distinguish between the mechanisms of acute pain and chronic neuropathic pain
- Employ an understanding of the manifestations of neuropathic pain in assessing patients experiencing chronic pain
- Identify the different classes of medications used to treat chronic pain and which medications are FDA-approved for specific neuropathic pain conditions
- Appraise the efficacy and safety outcomes of research on drugs recommended for treatment of chronic neuropathic pain when making treatment decisions
- Employ rational polypharmaceutical treatment strategies to maximize pain reduction and minimize adverse effects in patients experiencing chronic pain

Acute pain originates as a signal transmitted from the peripheral nervous system to the spinal cord by either A-delta or C-fibers. These impulses converge at the dorsal horn of the spinal cord and are routed on to 1 of the 2 ascending spinal cord tracts. The pain signal is then transmitted to the cerebral cortex, where it is perceived, localized, and interpreted.[1] Acute pain activates a complicated antinociceptive system which releases endorphins and enkephalins that trigger the release of gamma-aminobutyric acid (GABA), dynorphin, and other substances such as norepinephrine, oxytocin, and relaxin, which deactivate or inhibit pain transmission.[1]

Pathophysiology of Chronic Pain

In contrast to acute pain, chronic pain serves little functionality or protective purpose, persists despite healing after injury or disease, and ultimately interferes with normal activity and patient quality of life. One of the most common and troublesome types of chronic pain is neuropathic pain, which occurs when neural tissue is damaged by injury or disease. Damage to nerves can result in chronic pain which is often intractable.[4]

Neuropathic pain results from pathologic changes in the peripheral and/or central nervous system and serves no useful biologic function. It may become

TABLE 1

ESTIMATED PREVALENCE OF CHRONIC NEUROPATHIC PAIN CONDITIONS IN THE UNITED STATES

Condition	Number of Cases*
Low back pain–associated	2,100,000
Painful diabetic neuropathy	600,000
Postherpetic neuralgia	500,000
Cancer–associated	200,000
Spinal cord injury	120,000
Causalgia and reflex sympathetic dystrophy	100,000
Multiple sclerosis	50,000
Phantom pain	50,000
Poststroke	30,000
HIV-associated	15,000
Trigeminal neuralgia (tic douloureux)	15,000
Total (excluding back pain)	**1,765,000**
Total (including back pain)	**3,865,000**

*Based on a population of 270 million.

Bennett GJ. Neuropathic pain: new insights, new interventions. *Hosp Pract (Off Ed).* 1998;33:95-114.

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Product	Off-Label / Investigational Use*
Gabapentin	Sciatic-type pain
	HIV-related neuropathy
	Deafferentation neuropathy of the face
	Complex regional pain syndrome
	Painful diabetic neuropathy
Lidocaine patch 5%	Add on therapy for neuropathic pain syndromes
Opioids	Neuropathic pain
Methadone	Neuropathic pain
Tramadol	Neuropathic pain
Antidepressants	Painful diabetic neuropathy
Tricyclics	Neuropathic pain syndromes
Nortriptyline	Neuropathic pain
Desipramine	Neuropathic pain
Anticonvulsants	
Carbamazepine	Diabetic neuropathy
Lamotrigine	Neuropathic pain
Dextromethorphan	Neuropathic pain
Ketamine	Neuropathic pain
Memantine	Neuropathic pain

*__Open-label trial:__ A clinical trial in which clinicians and participants know the drug or vaccine is being administered. __Pilot study:__ The initial study examining a new method or treatment.

independent of, or dissociated from, the initial injury or damage, which results in a persistent pain state. In effect, chronic pain becomes a disease entity in and of itself. Neuropathic pain conditions include PDN, PHN, human immunodeficiency virus (HIV)-associated peripheral neuropathy, anesthesia dolorosa, phantom limb syndrome, and complex regional pain syndrome (CRPS). Patients with neuropathic pain often complain of **spontaneous** and/or **evoked** pain. Spontaneous pain, which is due to the sudden, unprovoked firing of axons or dorsal horn neurons,[5] can present as lancinating pain (usually paroxysmal), as constant burning pain, or as cramping/aching sensations.[3] Manifestations of evoked pain, which is caused by damage or alterations to peripheral and central sensory neurons, include **hyperalgesia** (a lowered threshold to painful stimuli), **allodynia** (pain evoked by normally innocuous stimuli, such as light touch or proprioception), and **hyperpathia** (an elevated threshold to painful stimuli with an explosive response that outlasts the stimulus).[6]

Peripheral and Central Mechanisms of Chronic Neuropathic Pain

Neuropathic pain has both peripheral and central origins. While the precise mechanisms for neuropathic pain remain to be identified, a number of theories based on scientific evidence have been advanced. In any one patient, more than one mechanism may be applicable or operative. Neuropathic pain can result from nerve trauma (eg, amputation), infection (eg, PHN), pressure (eg, tumor infiltration), infarct, metabolic disturbance (eg, diabetic neuropathy), or it may be idiopathic in nature.[7]

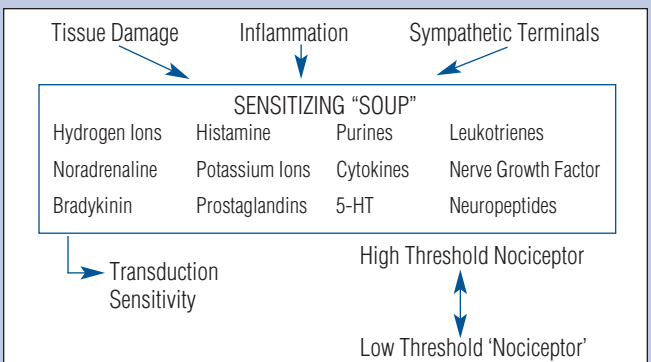
Peripheral Mechanisms

In the periphery, stimulus-independent pain can result from ectopic action potential discharge in the axon and cell body of injured sensory neurons.[8] These spontaneous ectopic discharges contribute to, and may result from, up-regulation or dysfunction of sodium channels in the damaged peripheral nerve fibers,[9] leading to sodium channel accumulation in areas of demyelination or axonal injury. The higher density of sodium channels in these areas can form foci of hyperexcitability.[8] This mechanism provides a rationale for treatment of neuropathic pain with sodium channel modulators such as lidocaine, carbamazepine, mexiletine, phenytoin, and tricyclic antidepressants.[4]

A complicating factor of neuropathic pain is **peripheral hypersensitivity** (ie, the increased sensitivity of peripheral nociceptors to external mechanical and thermal stimuli). Following tissue damage and its attendant peripheral nerve response (ie, pain), chemicals are released from blood vessels, from damaged and inflammatory cells (eg, macrophages, lymphocytes, and mast cells), and from the nociceptive nerve endings themselves.[10] The release of this "soup" of substances causes inflammation in the damaged area and can lead to local hypersensitivity. Peptides are released from nociceptive afferent fibers,[11] which result in an altered state of excitability in sensory and sympathetic nerve fibers, vasodilation, and plasma protein extravasation. This reaction in turn precipitates the release of chemical mediators from inflammatory cells.[10] These interactions can activate and sensitize high-threshold nociceptors that normally remain dormant, which results in peripheral sensitization[10] (Figure 1).[12] In addition, previously injured C-fibers can develop new adrenergic receptors, which increases their sensitivity to future stimulation.

FIGURE 1

PERIPHERAL SENSITIZATION



The sensitivity of high-threshold nociceptors can be modified in the periphery by a combination of chemicals that act as a "sensitizing soup." These chemicals are produced by damaged tissue as part of the inflammatory reaction and by sympathetic terminals.

5-HT = 5-hydroxytryptamine.

Reprinted with permission from Woolf CJ, Chong M-S. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg.* 1993;77:362-379.

Central Mechanisms

In addition to these peripheral responses, significant changes occur in the dorsal horn of the spinal cord. In the early stages following peripheral nerve injury, peripheral nociceptive fibers release a variety of neurotransmitters, particularly **glutamate** and **aspartate**, which are excitatory neurotransmitters that can bind to several different types of receptors.[13] Alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (**AMPA**) receptors, which are activated by glutamate, play a role in the sensation of acute pain and are always exposed on afferent nerve terminals.[1] The N-methyl-D-aspartate (**NMDA**) receptors are dormant until activated by persistent or large-scale release of glutamate.[14] Both AMPA and NMDA receptors, as well as others, play a significant role in the development of chronic pain. When AMPA receptors are continually activated, the postsynaptic membrane depolarizes, dislodging the magnesium ions that normally block the transmembrane

sodium and calcium ion channels of NMDA receptors. The resultant flux of cations further depolarizes the postsynaptic membrane potential, bringing it closer to the threshold potential for nerve impulse initiation.[15] This results in central hypersensitization, in that a low-intensity stimulus, which normally would not be strong enough to generate an action potential in the postsynaptic neuron, is now adequate to depolarize the membrane potential to threshold, initiating a pain impulse.[15] Additionally, significantly larger amounts of antinociceptive input are required to interrupt the impulse (ie, prevent the membrane potential from reaching threshold).[1] Under these conditions, naturally occurring pain relievers (eg, endorphins) lose their analgesic effectiveness and relatively higher doses of endogenous opioids are required to obtain an analgesic effect.[1] Thus, a much smaller stimulus is required to cause the sensation of pain, resulting in a chronic pain condition.

Additionally, neurokinins and substance-P interact with neurokinin receptors (NK1 and NK2), which lead to the influx of calcium into the cell.[14] Calcium acts as a critical second messenger: it activates nitric oxide, leads to immediate early gene expression, and phosphorylates a number of receptors at the level of the dorsal horn, which lowers its activation threshold and precipitates ectopic discharges, again resulting in central sensitization.[14]

The Rationale for a Mechanistic Approach to Neuropathic Pain Treatment

The overall aim of treatment for neuropathic pain is to improve patient function and quality of life with therapeutic approaches that reduce pain without inducing unacceptable side effects. The treatment paradigm includes the use of nonpharmacologic techniques (eg, relaxation, application of heat or cold, exercise, physical therapy, and cutaneous stimulation). However, while nonpharmacologic strategies may be useful in easing neuropathic pain and improving function when used as adjuncts to pharmacologic therapy,[16] they are rarely sufficient on their own, particularly in the case of chronic neuropathic pain. Pharmacotherapy is thus the primary intervention.

Because of the complex pathophysiology of neuropathic pain, it is often necessary to employ a mechanistic approach to drug selection, with less emphasis on therapeutic class stratification and greater attention to efficacy against the underlying cause.[14] This approach may allow for a more rational polymodal selection of therapeutic agents, and consequently, improved patient outcomes in the management of neuropathic pain.

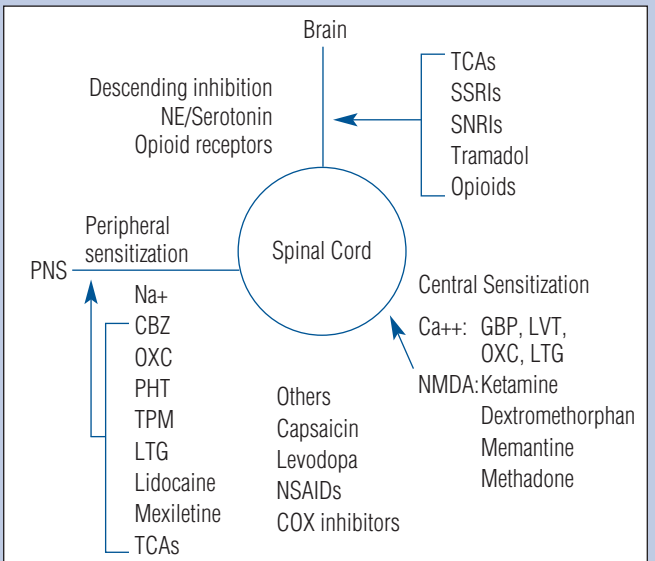
The actions of various pharmaceutical agents in the peripheral nervous system, spinal cord, and brain are depicted in Figure 2.[14] Many agents used to treat neuropathic pain are primarily indicated for other diseases such as depression, epilepsy, and arrhythmia.

Opioids, tramadol, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) exert their analgesic effect by enhancing the descending inhibitory pathways. Opioids activate receptors that result in inhibition of the release of neurotransmitters such as glutamate, substance-P, and acetylcholine.[14] Tramadol is a synthetic, atypical analgesic with low-affinity binding to mu-opioid receptors, and is a weak inhibitor of norepinephrine and serotonin reuptake.[17] Antidepressants provide pain relief by preventing the reuptake of biogenic amines, such as norepinephrine and serotonin, and by affecting agonist activity on alpha-2 adrenoreceptors.

Another means by which medications may produce analgesia is through modulation of central sensitization. Two groups of agents exert their effects in this way. The first group includes the anticonvulsants (eg, gabapentin, lamotrigine, levetiracetam, and oxcarbazepine). The anticonvulsants inhibit calcium flux primarily through the N-type channels, thereby blocking the activation of protein kinase C, phospholipase C, nitric oxide synthetase, and the induction of early gene expression, which have been implicated in the maintenance of central sensitization. In addition, lamotrigine and oxcarbazepine exert modulatory effects on voltage-gated sodium channels.[14] These agents are dually active at both central and peripheral sensitization sites.

FIGURE 2

MECHANISTIC STRATIFICATION OF MEDICATIONS USED TO TREAT NEUROPATHIC PAIN CONDITIONS



PNS = peripheral nervous system; CBZ = carbamazepine; OXC = oxcarbazepine; PHT = phenytoin; TPM = topiramate; LTG = lamotrigine; TCA = tricyclic antidepressants; NE = norepinephrine; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; GBP = gabapentin; LVT = levetiracetam; NMDA = N-methyl-D-aspartate; NSAIDs = nonsteroidal anti-inflammatory drugs; COX = cyclooxygenase.

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The second group is a diverse collection of agents with varied primary uses. These agents include dextromethorphan, a cough suppressant; ketamine, a dissociative anesthetic; memantine, an Alzheimer's and Parkinson's drug; and methadone, a synthetic opioid. These drugs modulate central sensitization via their effects on NMDA receptors. The use of these agents in humans for the treatment of neuropathic pain is still under study.[14]

In contrast to drugs that modulate central sensitization are those agents that can modulate peripheral sensitization by inactivating or blocking voltage-dependent sodium channels. These agents include, but are not limited to, carbamazepine, oxcarbazepine, topiramate, and lidocaine. By inactivating sodium channels, carbamazepine, oxcarbazepine, phenytoin, and topiramate inhibit the release of excitatory neurotransmitters and can reduce the high-frequency repetitive firing of nociceptive afferent fibers without affecting normal conduction. Lidocaine reversibly blocks and inactivates sodium channels, reducing the firing rate of damaged fibers. Capsaicin modulates peripheral sensitization via a different mechanism. It initially activates C-fiber nociceptors,[14] but leads to long-term desensitization of those receptors by destroying a subset of small-diameter primary afferent fibers and their cell bodies.

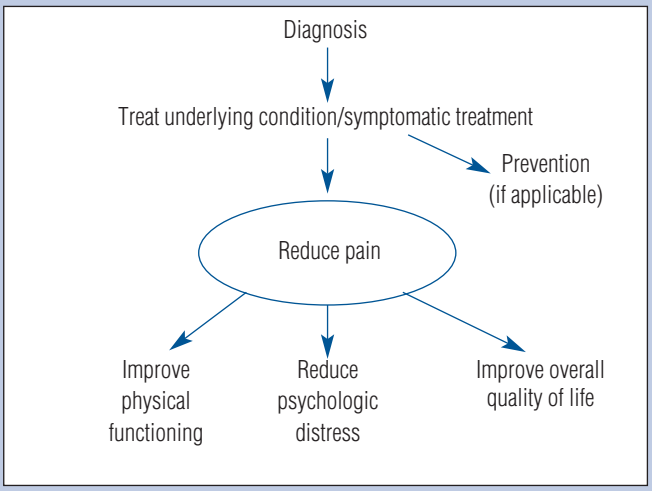
Clinical Management of Neuropathic Pain

Appropriate outcome expectations are key to the successful management of neuropathic pain. While long-standing pain is rarely eliminated, clinically meaningful goals such as reducing pain and associated psychological distress, and improving physical functioning and overall quality of life can be achieved in a considerable number of patients (Figure 3, page 4).[18]

The use of 2 or more agents with complementary mechanisms of action, known as multimodal therapy, is often required to achieve effective analgesia

FIGURE 3

NEUROPATHIC PAIN: APPROACH TO TREATMENT



Turk DC. Are pain syndromes acute or chronic diseases? *Clin J Pain.* 2000;16:279-280.

in chronic pain conditions.[19] The goal of treatment is to optimize pain relief while minimizing the risk of adverse effects and adverse drug interactions. This rational approach to polypharmacy suggests beginning with the least invasive approaches which have demonstrated efficacy, and adding to or substituting agents until adequate pain relief is achieved or intolerable side effects intervene.

A Mechanistic Approach to Treatment Selection

Medications approved by the Food and Drug Administration (FDA) for the treatment of neuropathic pain conditions include the lidocaine patch 5%, gabapentin, and pregabalin for the treatment of PHN; carbamazepine, which is indicated for trigeminal and glossopharyngeal neuralgias; and duloxetine and pregabalin for PDN. Other agents, including antidepressants, anticonvulsants, and antiarrhythmics, are all used with varying degrees of efficacy. In 2003, the *Archives of Neurology* published evidence-based treatment recommendations for neuropathic pain,[9] based on consensus proceedings from the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain. The agents recommended as first-line therapy, in the order given, are gabapentin, the lidocaine patch 5%, opioids, tramadol, and nortriptyline or desipramine (Table 2). These recommendations were based on a demonstration of efficacy in multiple randomized controlled clinical trials. Additional agents, including other anticonvulsant medications such as

TABLE 2

FIRST-LINE MEDICATIONS FOR NEUROPATHIC PAIN

Medication	Initial Dosage	Titration	Maximum Dosage	Duration of Adequate Trial	Most Common Adverse Effects
Gabapentin	100 to 300 mg every night or 100 to 300 mg tid	↑ by 100 to 300 mg tid every 1 to 7 days as tolerated	3600 mg/d (reduce if low CrCl)	3 to 8 weeks for titration plus 1 to 2 weeks at maximum tolerated dosage	• Somnolence • Dizziness • GI symptoms • Peripheral edema
Lidocaine patch 5% (topical)	≤ 3 patches daily for ≤12 hours	None needed	3 patches daily for ≤12 hours	2 weeks	• Mild skin reactions (erythema, rash) • Systemic absorption must be considered in patients receiving oral class 1 antiarrhythmic drugs
Opioids*	5 to 15 mg every 4 hours as needed	After 1 to 2 weeks, convert total daily dosage to long-acting opioid and continue short-acting medication as needed	No maximum with careful titration; consider pain-specialist evaluation at dosages >120 to 180 mg daily	4 to 6 weeks	• Constipation • Sedation • Nausea
Tramadol	50 mg once/twice daily	↑ by 50 to 100 mg daily in divided doses every 3 to 7 days as tolerated	400 mg daily	4 weeks	• Dizziness • Nausea • Constipation • Somnolence • Orthostatic hypotension
Nortriptyline or desipramine	10 to 25 mg every night	↑ by 10 to 25 mg daily every 3 to 7 days as tolerated	75 to 150 mg daily (continue titration with caution if blood level of drug + metabolite is <100 ng/mL)	6 to 8 weeks, with ≥1 to 2 weeks at maximum tolerated dosage	• Adverse cardiac events • Urinary retention • Sedation • Anticholinergic effects • Orthostatic hypotension

*Dosages given are for morphine sulfate.

CrCl = creatinine clearance; GI = gastrointestinal.

Adapted with permission from Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol.* 2003;60:1524-1534.

lamotrigine and carbamazepine, and other antidepressants such as bupropion, citalopram, paroxetine, and venlafaxine, are recommended when use of the first-line medications alone or in combination do not result in a satisfactory response in the patient.[9] In late 2004, after these recommendations were published, 2 newer agents, pregabalin and duloxetine, were also approved by the FDA for treatment of neuropathic pain.[20,21] The scope of this paper will focus on only approved or recommended first-line pharmacotherapy for neuropathic pain.

Gabapentin

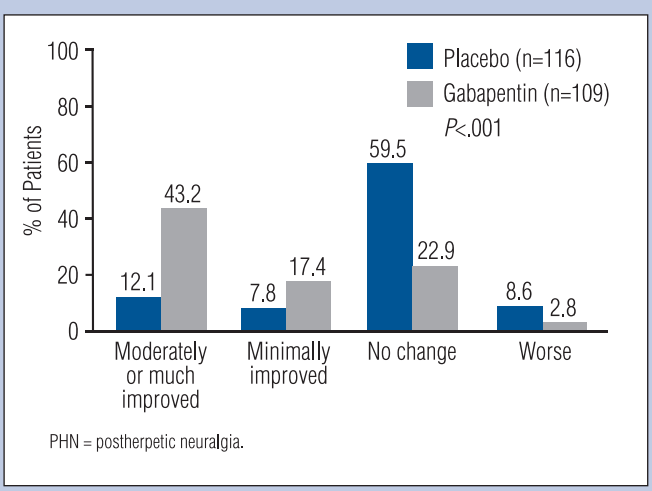
Many antiepileptic and antidepressant drugs, including gabapentin, pregabalin, and duloxetine, have been studied for treatment of chronic, noncancer pain.[22] Gabapentin is FDA-approved for the management of PHN and epilepsy. Its efficacy has also been documented in the treatment of various neuropathic pain states, including sciatic-type pain, HIV-related neuropathy, deafferentation neuropathy of the face, complex regional pain syndrome,[23] and PDN.[24] The mechanisms by which gabapentin exerts its analgesic and anticonvulsant actions is somewhat unclear; however, it appears to bind to specific, unevenly distributed sites throughout the brain. The highest concentration of these sites is in the cerebral cortex, and the lowest is in the white matter. These binding sites appear to be localized to neuronal cell bodies in the regions of the brain associated with excitatory amino acid input.[25]

Gabapentin may cause or exacerbate gait and balance problems, or cause cognitive impairment in elderly patients. Dosage adjustments are necessary in patients with renal insufficiency.[9] Adverse effects of gabapentin can include somnolence, dizziness, and less commonly, gastrointestinal symptoms, as well as mild peripheral edema. These are generally mild to moderate in nature,[26] and gabapentin is relatively well tolerated when dosed in a gradually escalating regimen.

The efficacy of gabapentin for neuropathic pain has been demonstrated in multiple randomized controlled trials. One of the pivotal trials was a randomized, double-blind, placebo-controlled clinical trial of 229 patients with PHN conducted by Rowbotham and colleagues.[27] Participants received 8 weeks of treatment with either gabapentin titrated to a maximum of 3600 mg/d, or a matching placebo. The proportion of patients treated with gabapentin who reported themselves improved on the Subjects' Global Impression of Change at the end of treatment was significantly greater than the proportion of patients treated with placebo (Figure 4).[27]

FIGURE 4

SUBJECTS WITH PHN REPORTING IMPROVEMENT OF PAIN IN ASSOCIATION WITH GABAPENTIN AND WITH PLACEBO



PHN = postherpetic neuralgia.

Reprinted from Rowbotham M, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280:1837-1842.

In an 8-week randomized, double-blind, placebo-controlled clinical trial of gabapentin for the treatment of the pain associated with diabetic neuropathy, patients who received gabapentin reported significantly less pain at weeks 2 through 8 than those who received a placebo. The primary end point was mean daily pain severity, measured on an 11-point Likert scale.[24]

Lidocaine Patch 5%

The lidocaine patch 5% is the only peripherally active agent indicated for the treatment of PHN. It exerts its analgesic effect without producing local anesthesia (ie, without inducing numbness) presumably by delivering sufficient amounts of lidocaine to block sodium channels on small damaged/dysfunctional pain fibers but insufficient to block sodium channels on large, myelinated A-β sensory fibers.[28] Currently approved dosing is up to 3 patches applied for 12 hours on/12 hours off. Recent pharmacokinetic and open-label pilot studies suggest 4 patches applied for 18 hours per day are safe,[29] with an adverse event profile that is not appreciably different from that found when the FDA-approved dosage is used.[30] As a topical agent, the lidocaine patch results in clinically insignificant blood levels of lidocaine, and as such is generally safe and well tolerated. The most common adverse events associated with its use are mild erythema or rash at the site of placement.[31]

There are 3 published double-blind, randomized, vehicle-controlled clinical trials of the lidocaine patch 5% in patients with PHN and other peripheral neuropathic pain syndromes.[32-34] In all 3 of these studies, patients who received active treatment obtained significantly greater pain relief than those who received a vehicle (nonactive) patch.

A randomized, double-blind, vehicle-controlled, 3-week efficacy study of the lidocaine patch 5% was conducted in patients with PHN to determine the efficacy of the patch for distinct neuropathic pain qualities common to multiple neuropathic pain conditions.[35] Only patients who reported moderate-to-severe pain on the Neuropathic Pain Scale (NPS) (defined as a score of greater than or equal to 4/10) reported for at least 6 of the 10 individual NPS items were eligible for the study. After 3 weeks of treatment, the use of the lidocaine patch 5% reduced the intensity of all common neuropathic pain qualities, and improved all assessed pain qualities to a greater extent than the vehicle patch, as measured by the sum score of the NPS.

The lidocaine patch 5% has also demonstrated efficacy as an add-on therapy to concomitant oral pain medication. In a prospective, randomized, vehicle-controlled, 2-way crossover study of patients with peripheral neuropathic pain syndromes, Meier and colleagues found significant decreases in ongoing pain intensity ($P<.001$) (Figure 5a, page 6) and allodynia ($P<.001$) (Figure 5b, page 6), and a statistically significant reduction of neuropathic symptoms ($P=.032$).[32]

Opioids

Although the evidence-based neuropathic pain treatment recommendations suggest the use of opioid analgesics as a first-line treatment option, the guidelines also acknowledge that the use of opioids generally requires some caution,[9] and in clinical practice, some controversies exist as to the most appropriate use of opioids for neuropathic pain. Therefore, a brief overview of their various mechanisms of action, efficacy, and principles of prescribing is essential. Table 3, page 6 lists commonly used opioid analgesics.

While neuropathic pain has traditionally been considered "less responsive" to opioid therapy, controlled clinical trials and clinical experience suggest that there may be a subpopulation of patients with chronic pain who may benefit from treatment with opioid analgesics.[19] Five double-blind randomized trials of oral opioid analgesics for the treatment of neuropathic pain have been published since 1998.[36-40] The results of these studies provide reliable evidence that opioids should be considered as a treatment option for neuropathic pain.[9]

Opioids act on both central and peripheral mu, kappa, and delta opioid receptors, which block the repeated transmission of nociceptive input from the periphery to the spinal cord. They also activate descending inhibitory pathways that modulate transmission of pain impulses in the spinal cord, and

FIGURE 5A

CHANGE FROM BASELINE IN ONGOING PAIN FOR THE INITIAL 8 HOURS AND 7-DAY TREATMENT PERIOD COMPARING THE LIDOCAINE PATCH 5% WITH PLACEBO IN PATIENTS WITH NEUROPATHIC PAIN (N=40)

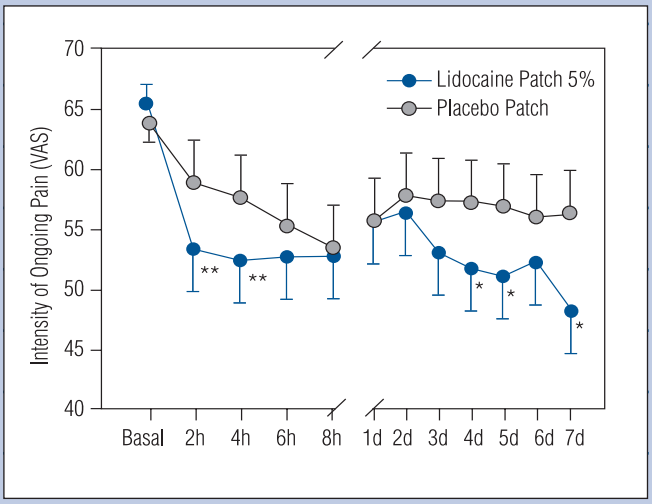
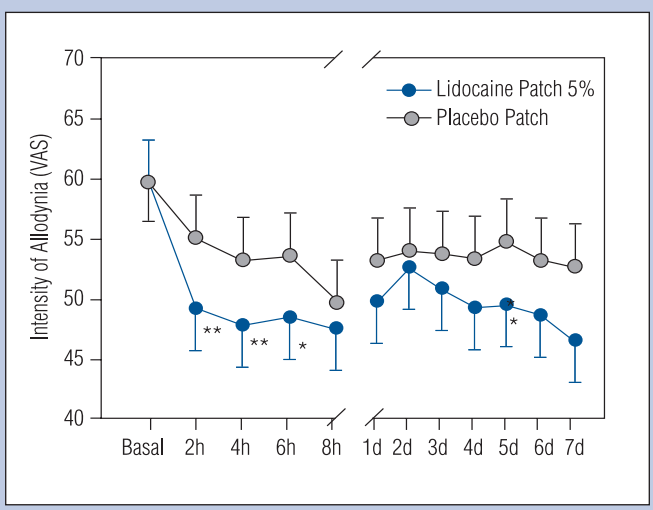


FIGURE 5B

CHANGE FROM BASELINE IN ALLODYNIA FOR THE INITIAL 8 HOURS AND 7-DAY TREATMENT PERIOD COMPARING THE LIDOCAINE PATCH 5% WITH PLACEBO IN PATIENTS WITH NEUROPATHIC PAIN (N=40)



Change of basal scores (VAS) (a) ongoing pain, (b) allodynia throughout the first 8 h and 7-day treatment period after patch application; mean (±SEM); lidocaine patch vs placebo patch. *P<.05 and **P<.01; N=40. The decrease in ongoing pain intensity and allodynia was highly significant in the lidocaine group (P<.001) and significant in the placebo group (P<.05) compared with the pretreatment (basal) values at all time points of the assessment.

VAS = visual analog scale; SEM = standard error of mean.

Reprinted with permission from International Association for the Study of Pain®. Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain.* 2003;106:155.

alter limbic system activity.[41-43] Opioids are classified as full agonists, partial agonists, or mixed agonist-antagonists, depending on their intrinsic activity at the various receptors to which they bind.[44]

TABLE 3

COMMONLY USED OPIOID ANALGESICS

Agent	Routes of administration	Duration of action (hours)
Morphine	IM, PO, PR	3-4
	TR PO	24
Codeine	PO	3-6
	IM	3-4
Hydromorphone	PO, PR	3-4
	IM	3-6
	TR	24
Methadone	PO, IM	4-8
Hydrocodone	PO	3-6
Oxycodone	PO	3-6
	TR PO	8-12
Oxymorphone	IV	3-6
	PR	4-6
Levorphanol	PO	4-5
	IM	4-5
Fentanyl	Transdermal patch	48-72

IM = intramuscular; PO = oral; TR = timed release; PR = rectal; IV = intravenous.

Cherny NI. The management of cancer pain. *CA Cancer J Clin.* 2000;50:70-116.

Way WL, Fields HL, Schumacher MA. Opioid analgesics & antagonists. In: Katzung BG, ed. *Basic & Clinical Pharmacology.* 8th ed. New York, NY: McGraw-Hill; 2001:512-531.

The most commonly used full agonists exert their action at the mu-opioid receptor and include morphine, hydromorphone, codeine, oxycodone, oxymorphone, hydrocodone, levorphanol, fentanyl, and methadone. Full agonists mimic the action of endogenous opioids most closely, and their efficacy is dose dependent. Morphine is generally regarded as the reference drug for full mu agonists. Full agonists do not have a ceiling effect, and will not reverse or antagonize the effects of other opioids within this class, if given simultaneously[45]; however, they should not be given concomitantly with a mixed agonist-antagonist, as this may precipitate withdrawal and cause increased pain.

Buprenorphine, an example of a partial agonist, has less effect at opioid receptors, and displays a ceiling effect to analgesia. Mixed agonist-antagonists in clinical use are pentazocine, butorphanol, and nalbuphine; however, they also possess a ceiling effect, and generally play a minor role in the management of chronic pain.[44]

Tramadol, a weak mu agonist, is among the agents recommended as first-line treatment for neuropathic pain.[9] Although its mechanism of action is not completely understood, it appears to function through the binding of the parent drug and the metabolite M1 to mu-opioid receptors, weakly inhibiting the reuptake of norepinephrine and serotonin.[46] Two published, double-blind, placebo-controlled, randomized clinical trials have demonstrated the usefulness of tramadol in the treatment of neuropathic pain. These studies demonstrated improvement in pain, as well as beneficial effects on allodynia and quality of life[17,47]; however, seizures have been reported within the normal dosage range (100-400 mg/d). Postmarketing reports show an increased risk of seizures with doses above the recommended range. In addition, concomitant use of tramadol increases the risk of seizures in patients taking SSRIs, TCAs, and other opioids.[46]

Principles of Opioid Prescribing for Chronic Neuropathic Pain

The potential risks of misuse, diversion, and addiction, as well as side effects and drug interactions, suggest that the prescription of opioids for chronic pain should be guided by rigorous principles. It is critical that primary care

clinicians have a clear understanding of the distinction between addiction, tolerance, physical dependence, and pseudoaddiction (Table 4).[48]

When chronic opioid therapy is being considered, the patient's pain should be assessed and relative abuse potential should be considered, both through a detailed history, through periodic reassessments, and through additional insights that may be obtained via specific screening aids such as the Screener and Opioid Assessment for Patients with Pain (SOAPP).[49] In addition, documentation of the treatment plan and its proposed outcomes, by the use of a patient agreement, is advised. Patient agreements are typically used for clarifying descriptions and expectations of medication use and abuse, consequences of violating the agreement, the procedure for discontinuing opioid therapy, educational and administrative issues, and terms for adherence monitoring.[50] It is also important to prevent and control side effects with specific management techniques (ie, stimulant laxatives for prevention of constipation). If analgesia is inadequate or side effects are unmanageable, a different opioid or an alternative route of administration can be attempted. Because of interpatient variability in analgesic responses and side effects, sequential trials of other opioids (referred to as opioid rotation) may often be necessary to identify the opioid that offers the best balance between effective analgesia and manageable side effects.[51]

Many opioids possess the potential for interaction with drugs that are metabolized by cytochrome P450 (CYP450) enzyme activity.[52] A number of commonly used pharmacologic agents, such as certain antidepressants, antipsychotics, antihypertensives, and antihistamines, affect CYP450 enzyme activity.[53]

TABLE 4

DEFINITIONS RELATED TO THE USE OF OPIOIDS FOR THE TREATMENT OF PAIN

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

Pseudoaddiction is a term that has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when pain is effectively treated.

Physical Dependence is a state of adaptation that often includes tolerance and is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. In the case of sedative drugs, spontaneous withdrawal may occur with continued use.

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

American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine. Consensus Document: Definitions related to the use of opioids for the treatment of pain. Available at: http://www.ampainsoc.org/advocacy/opioids2.htm. Accessed May 27, 2005.

Tricyclic Antidepressants

TCAs are commonly used for the treatment of neuropathic pain. They are divided into 2 major groups: tertiary amines, such as amitriptyline, and secondary amines, such as nortriptyline. Although the precise action of tricyclic antidepressants is not fully understood, the putative analgesic mechanism is that tertiary amines inhibit reuptake of the biogenic amines (mostly norepinephrine), as well as serotonin. The secondary amines are relatively selective norepinephrine reuptake inhibitors.[54] Additionally, amitriptyline, doxepin, and desipramine are strong sodium channel modulators.[55]

TCAs are often used in the treatment of PDN and other neuropathic pain syndromes. Traditionally, it was believed that TCAs were most effective for treating constant pain, and that carbamazepine-like anticonvulsants should be used to treat lancinating pain; however, recent trials have shown no evidence of a difference in treatment response.[9] A representative summary of the overall efficacy of TCAs in the treatment of neuropathic pain is illustrated by 2 randomized, double-blind, crossover studies that compared desipramine (secondary amine), amitriptyline (tertiary amine), and fluoxetine (SSRI) (versus placebo) in patients with PDN.[56]

Results showed that 74% of amitriptyline-treated patients experienced moderate or significant pain relief compared with 61% of desipramine-treated patients and 48% of fluoxetine-treated patients; however, when fluoxetine was compared with placebo, 41% of placebo-treated patients also had moderate or significant pain relief. In the final analysis, patients who received amitriptyline or desipramine had significant decreases in pain compared to placebo, but no statistically significant differences were found between fluoxetine and placebo. These results do not support the use of SSRIs in the treatment of neuropathic pain, except in patients with corresponding depression.[56]

The use of TCAs in neuropathic pain is limited by their side-effect profiles, which include sedation, urinary retention, or postural hypotension. The sedative effects associated with these agents can lead to falls, especially in older adults. TCAs should be used with caution in patients with cardiovascular disease, and a screening electrocardiogram to check for cardiac conduction abnormalities is recommended prior to treatment, especially in patients over 40 years of age.[9]

Carbamazepine

Carbamazepine is approved by the FDA for the treatment of trigeminal neuralgia. Some evidence also exists for the use of carbamazepine in patients with PDN, but studies on this condition conducted over 20 years ago do not meet current methodologic standards.[9] Carbamazepine can be recommended for patients who have not responded to gabapentin.[9] It is prescribed in doses ranging from 600 to 1200 mg/d that are given in 3 or 4 divided doses.[57]

Carbamazepine is structurally related to the TCAs. Its mode of action is to enhance inactivation of voltage-gated sodium channels, thereby reducing high-frequency repetitive firing of action potentials.[14] The concentration-response curve of carbamazepine suggests that this compound binds to one receptor at or near the sodium channel, and has a higher affinity for the inactivated channel conformation.[58] Carbamazepine diminishes the release of excitatory neurotransmitters as a by-product of its effects on the sodium channels, and has been found to modulate the high-threshold L-type calcium channels. Other mechanisms of action for carbamazepine are increased release of serotonin and enhanced dopaminergic transmission.[14] Carbamazepine's use may be limited due to a wide range of side effects which include sedation, ataxia, dizziness, diplopia, nausea, and dyspepsia and can be minimized by starting with low doses. More serious, but less common adverse effects include blood dyscrasias, bone marrow suppression, and effects on liver. Carbamazepine should be used with caution in those patients on other immunosuppressive agents (eg, chemotherapy, radiation therapy). Baseline and periodic complete blood count and liver function tests must be performed in all patients during treatment with carbamazepine.[59]

Recently Approved Agents

Although not addressed in the above recommendations,[9] pregabalin and duloxetine have recently been approved by the FDA for treatment of PDN (both agents) and PHN (pregabalin). As these agents have not been used extensively for treatment of chronic pain conditions, little or no postmarketing data are available.

Pregabalin is a substituted analogue of GABA, and is related to gabapentin. It was approved for treatment of PHN and PDN. The exact mechanism of action of pregabalin is unclear, but it may reduce excitatory neurotransmitter release by binding to voltage-gated calcium channels.[60] In 3 randomized, double-blind, placebo-controlled, multicenter studies, oral pregabalin was superior to placebo in relieving pain and pain-related sleep interference in patients with PHN.[9,61] It was also found to improve daily mean pain scores in 2 other studies.[60]

In patients with PDN, pregabalin also reduced pain and pain-related sleep disorders in 3 other randomized, double-blind, placebo-controlled, multicenter studies.[61] In these studies, pregabalin was well tolerated in both PHN and PDN patients, with dizziness, somnolence, and peripheral edema the most common adverse events.[60,61]

Duloxetine, approved for treatment of depression prior to approval for treatment of PDN, is a potent and balanced inhibitor of both serotonin (5-HT) and norepinephrine (NE) reuptake, possessing comparable binding affinities for NE and 5-HT transport sites.[62] Not only do 5-HT and NE play an important role in the regulation of mood, but they are recognized as key modulatory neurotransmitters in the descending pain pathways that inhibit afferent pain fibers ascending through the spinal cord.[63] This may, therefore, be an important regulatory system for endogenous pain control, and the combined activity of 5-HT and NE appears to result in the maintenance of a pain threshold and a reduction of pain sensitivity.[64]

In clinical trials, people treated with duloxetine reported less pain compared with those given placebo.[65] Fifty-eight percent of people treated with duloxetine reported at least a 30% sustained reduction of pain, compared with 34% of people treated with a placebo. The most commonly reported side effects were nausea, dry mouth, constipation, and diarrhea. In some cases, patients experienced dizziness and hot flashes.[65]

Conclusion

Chronic neuropathic pain is the cause of significant morbidity in a large proportion of the population. The etiology of chronic pain is diverse and multifactorial; specific and effective treatment regimens remain elusive. Therefore, it is critical that clinicians understand its complex pathophysiology in order to make informed treatment decisions. Pharmacotherapy is the cornerstone of management for patients with chronic neuropathic pain. Employing rational polypharmaceutical strategies will better balance the objectives of maximizing pain reduction and minimizing the adverse effects.

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BREAKTHROUGHS AND CHALLENGES IN THE MANAGEMENT OF COMMON CHRONIC PAIN CONDITIONS: A FOCUS ON NEUROPATHIC PAIN

PENNSTATE
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ANSWER SHEET, PROGRAM EVALUATION, AND CME CREDIT REQUEST

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POSTTEST

1. Which of the following is not a manifestation of evoked pain, which is caused by damage or alterations to peripheral and central sensory neurons?
   a. Hyperalgesia
   b. Hyperneuralgia
   c. Allodynia
   d. Hyperpathia

2. In peripheral hypersensitivity:
   a. Tissue damage and its attendant peripheral nerve response release chemicals from blood vessels, from damaged and inflammatory cells, and from the nociceptive nerve endings.
   b. Peptides are released from nociceptive afferent fibers, which result in an altered state of excitability in sensory and sympathetic nerve fibers, vasodilation, and plasma protein extravasation.
   c. Previously injured C-fibers cannot develop new adrenergic receptors, which would increase their sensitivity to future stimulation.
   d. Both a and b
   e. Both b and c

3. In the early stages following peripheral nerve injury, peripheral nociceptive fibers release a variety of neurotransmitters, particularly:
   a. Glutamate and aspartate.
   b. Dopamine and serotonin.
   c. Calcium and neurokinin.
   d. Neurokinin and substance-P.

4. Many agents used to treat neuropathic pain are primarily indicated for other diseases such as:
   a. Parkinson's disease, depression, and irritable bowel syndrome.
   b. Depression, epilepsy, and arrhythmia.
   c. Epilepsy and attention deficit.
   d. Arrhythmia and diabetes.

5. Opioids, tramadol, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) exert their analgesic effect by:
   a. Inhibiting the release of neurotransmitters such as glutamate, substance-P, and acetylcholine.
   b. Enhancing the descending inhibitory pathways.
   c. Modulating central sensitization.
   d. Affecting agonist activity on alpha-2 adrenoreceptors.

6. Carbamazepine, oxcarbazepine, topiramate, lidocaine, and capsaicin all belong to a group of drugs that:
   a. Modulate central sensitization via their effects on NMDA receptors.
   b. Exert modulatory effects on voltage-gated sodium channels.
   c. Weakly inhibit norepinephrine and serotonin reuptake.
   d. Modulate peripheral sensitization by inactivating voltage-dependent sodium channels.

7. Which medication below is not approved by the Food and Drug Administration (FDA) for the treatment of the listed neuropathic pain conditions?
   a. Carbamazepine, for trigeminal and glossopharyngeal neuralgias.
   b. The lidocaine patch 5%, for PHN.
   c. Gabapentin, for PHN.
   d. All are FDA-approved for those conditions.

8. If analgesia is inadequate or side effects are unmanageable, opioids should be discontinued, and a different opioid or an alternative route of administration should not be attempted.
   a. True b. False

9. Traditionally, tricyclic antidepressants were considered most effective for treating constant pain, while carbamazepine-like anticonvulsants were considered appropriate for treating lancinating pain; however, recent trials have shown no evidence of a difference in treatment response.
   a. True b. False

10. Continuing advances in our understanding of the pathophysiologic mechanisms of chronic pain, and recently published, evidence-based guidelines suggest that the management of neuropathic pain may be improved through the use of:
    a. A multimodal approach to treatment.
    b. Nonpharmaceutical approaches to treatment.
    c. A mechanistic approach to treatment.
    d. Both b and c
    e. Both a and c

POSTTEST ANSWERS/PROGRAM EVALUATION

Please record your posttest answers:

1.___ 2. ___ 3. ___ 4. ___ 5. ___ 6. ___ 7. ___ 8. ___ 9. ___ 10. ___

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   O I need more information before I can change my practice behavior.
   O I will immediately implement the information in my practice.

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