

## Management of Neuropathic Pain

Katherine E. Galluzzi, DO



Pain may be the most common reason patients seek treatment from physicians. When persistent and unrelieved, pain can frustrate both the person suffering with this condition and the physician trying to alleviate it. Relief from chronic pain may be particularly difficult to achieve and fraught with misconceptions. Treatment usually requires trials of physical, pharmacologic, and surgical interventions to achieve resolution. In cases that remain insoluble, patients must accept partial relief and seek adaptive strategies.

The source of persistent pain may be nociceptive or neuropathic. Both utilize the same nervous system pathways for transmission, but significant physiologic differences exist in the mechanism through which the body processes and resolves these painful stimuli. Nociceptive pain that results from a known or obvious source (eg, trauma, cancer metastasis, ischemia, arthritis) is often easy to identify. Neuropathic pain, however, may occur in the absence of an identifiable precipitating cause. Physicians must remain alert to differences in presentation and course of neuropathic pain syndromes, some of which may be subtle or unusual.

The International Association for the Study of Pain defines neuropathic pain as “initiated or caused by a primary lesion or dysfunction in the nervous system” and due to disordered peripheral or central nerves.<sup>1</sup> The disorder can be caused by compression, transection, infiltration, ischemia, or metabolic injury to neuronal cell bodies, or in combination. Neuropathic pain may be classified

as either peripheral or deafferentation (central) in origin.<sup>2</sup> Examples of the former include diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), antineoplastic therapy- or HIV-induced sensory neuropathy, tumor infiltration neuropathy, phantom limb pain, postmastectomy pain, complex regional pain syndromes (reflex sympathetic dystrophy), and trigeminal neuralgia. Deafferentation syndromes resulting in neuropathic pain include multiple sclerosis (MS), spinal cord injury (SCI), central poststroke pain, and Parkinson disease.

Bennett<sup>3</sup> provided incidence estimates of common types of neuropathic pain and concluded that if neuropathic low back pain is included in the total, approximately 3.8 million individuals in the United States alone suffer from this disorder. Bowsher<sup>4</sup> calculated that there might be as many as 1 million patients with PHN in the United States. Such painful conditions are likely to increase as the population continues to age; eg, herpes zoster, diabetes mellitus, cerebrovascular accidents, Parkinson disease, and cancer are diseases of aging.

Diabetic peripheral neuropathy, second only to low back pain-associated neuropathy, is estimated to account for 600 cases per 100,000 (Table 1); these cases are certain to increase as the population of those with diabetes mellitus continues to increase.

### Neuropathic Versus Nociceptive Pain

Response to an acute painful stimulus is an important adaptive mechanism that protects a person from further injury. Considering characteristics that nociceptive and neuropathic pain have in common will help clarify their differences. Pain signals resulting from noxious stimuli (wounds, thermal or inflammatory insults) are converted into electrical impulses within tissue nociceptors whose cell bodies are found in dorsal root ganglions; both nociceptive and neuropathic pain signals utilize the same pain pathways.

Information regarding intensity, quality, and location of pain is conveyed to the sensory cortex from the somatosensory thalamus. The central nervous system utilizes descending inhibitory pathways via the dorsolateral fasciculus (Lissauer's tract) of the spinal cord and the periaqueductal gray matter to modulate transmission of nociceptive stimuli.<sup>5,6</sup> Namaka et al<sup>7</sup> characterize this as a complex equilibrium of pain-signaling and pain-relieving pathways connecting peripheral and central nervous systems.

Efficient, rapid transmission of acute responses to a painful stimulus is a self-

Address correspondence to Katherine E. Galluzzi, DO, CMD, FACOPF *distinguished*, Professor and Chair, Department of Geriatric Medicine, Philadelphia College of Osteopathic Medicine, 4190 City Ave, Suite 315, Philadelphia, PA 19131-1633.

Dr Galluzzi is on the speakers bureaus of Pfizer Inc and Purdue Pharma LP.

E-mail: katherineg@pcom.edu

This continuing medical education publication supported by an unrestricted educational grant from Purdue Pharma LP

protection process. Pain signals an “alarm” that leads to subsequent protective responses. Neuropathic pain, however, signals no imminent danger. The operative difference is that neuropathic pain represents a delayed, ongoing response to damage that is no longer acute which continues to be expressed as painful sensations.

Sensory neurons damaged by injury, disease, or drugs produce spontaneous discharges that lead to sustained levels of excitability. These ectopic discharges begin to “cross talk” with adjacent uninjured nerve fibers, resulting in amplification of the pain impulse (peripheral sensitization). This hyperexcitability leads to increased transmitter release causing increased response by spinal cord neurons (central sensitization). The process, known as “windup,” accounts for the fact that the level of perceived pain is far greater than what is expected based on what can be observed.<sup>8,9</sup>

Painful nerve stimulation leads to activation of N-methyl-D-aspartate (NMDA) receptors on the postsynaptic membrane in the dorsal horn of the spinal cord.<sup>6(pp207-228)</sup> Release of NMDA, a modulating neurotransmitter, is coupled with subsequent release of glutamate, an excitatory neurotransmitter. The resultant extended depolarization (influx of calcium and sodium and efflux of potassium) produces much larger than usual postsynaptic potentials, known as *synaptic potentiation*. Spinal windup has been described as “continuous increased excitability of central neuronal membranes with persistent potentiation”<sup>9,10</sup> Neurons of the peripheral and central nervous system continue to transmit pain signals beyond the original injury, thus activating an ongoing, continuous central pain response (Figure 1). Devor et al<sup>11</sup> presented evidence showing that damaged sensory fibers have a higher concentration of sodium channels, an alteration that would increase spontaneous firing.

### Characterization of the Pain

The symptoms described by persons with neuropathic pain are myriad (see *Sidebar*, p S15), representing a variety of possible nerve injuries implicated in the etiology.<sup>2</sup> Neuropathic pain sufferers complain of numbness, burning, or tin-

**Table 1**  
Estimated Prevalence of Neuropathic Pain in the United States\*

Condition	No. per 100,000
<input type="checkbox"/> Diabetic peripheral neuropathy	600
<input type="checkbox"/> Postherpetic neuralgia	500
<input type="checkbox"/> Cancer-associated	200
<input type="checkbox"/> Spinal cord injury	120
<input type="checkbox"/> Causalgia and reflex sympathetic dystrophy	100
<input type="checkbox"/> Multiple sclerosis	50
<input type="checkbox"/> Phantom pain	50
<input type="checkbox"/> Poststroke	30
<input type="checkbox"/> HIV-associated	15
<input type="checkbox"/> Trigeminal neuralgia (tic douloureux)	15
<input type="checkbox"/> Low-back pain-associated	2,100
<b>Total (excluding back pain)</b>	<b>1,680 M</b>
<b>Total (including back pain)</b>	<b>3,780 M</b>

\* Based on population of 270 million.

† Source: Bennett GJ. Neuropathic pain: new insights, new interventions. *Hosp Pract (Off Ed)*. October 15, 1998;33(10):95-98, 101-104, 107-110 passim.

**Table 2**  
Sensory Symptoms and Signs Associated With Neuropathic Pain

Symptom or Sign	Description
■ <b>Allodynia</b>	Pain due to nonnoxious stimuli (clothing, light touch) when applied to the affected area. May be mechanical (eg, caused by light pressure), dynamic (caused by nonpainful movement of a stimulus), or thermal (caused by nonpainful warm, or cool stimulus)
■ <b>Anesthesia</b>	Loss of normal sensation to the affected region
■ <b>Dysesthesia</b>	Spontaneous or evoked unpleasant abnormal sensations
■ <b>Hyperalgesia</b>	Exaggerated response to a mildly noxious stimulus applied to the affected region
■ <b>Hyperpathia</b>	Delayed and explosive response to a noxious stimulus applied to the affected region
■ <b>Hypoesthesia</b>	Reduction of normal sensation to the affected region
■ <b>Paresthesias</b>	Nonpainful spontaneous abnormal sensations
■ <b>Phantom Pain</b>	Pain from a specific site that no longer exists (eg, amputated limb) or where there is no current injury
■ <b>Referred Pain</b>	Occurs in a region remote from the source

gling, or a combination; they describe electric shock-like, prickly, or pins and needles sensations. In 1990, Boureau et al<sup>12</sup> identified six adjectives used substantially more frequently to describe neuropathic pain. *Electric shock, burning, and tingling* were most commonly used (53%, 54%, and 48% respectively), in addition to *cold, pricking, and itching*. These terms should suggest a neuropathic etiology for pain.

Several common types of responses are elicited from patients with neuropathic pain (Table 2). These abnormal sensations, or dysesthesias, may occur alone, or they may occur in addition to other specific complaints. Unlike the usual response to nociceptive pain, the irritating or painful sensation occurs completely in the absence of an apparent cause. A common example is the severe, aching, “toothache-like” response elicited by a cool draft of air on the cheek of a patient suffering from trigeminal neuralgia.

*Allodynia* is the term given to a painful response to an otherwise benign stimulus. Taken to the extreme (eg, inability to remove the stimulus), this response can result in the agonizing neuropathic symptom known as *hyperpathia*. Another example of allodynia is touch sensitivity of badly sunburned skin, where even light stroking of the inflamed area causes extreme discomfort; like neuropathic pain, this response seems out of proportion to the injury.

With respect to anesthesia or hypoesthesia, pharmacologic induction of this condition by lidocaine hydrochloride or fentanyl produces predictable half-lives and duration of action; this is not the case with neuropathic-induced anesthesia or hypoesthesia. The discomfort of one’s foot “falling asleep” is a common paresthesia. That uncomfortable sensation is self-limiting and resolves spontaneously, unlike the continuous, self-perpetuating and annoying sensation of pins and needles caused by neuropathic pain.

### Pain Scales for Assessing Neuropathic Pain

Scales have been developed to assess pain. Since the Joint Commission on Accreditation of Healthcare Organizations adopted pain as “the fifth vital

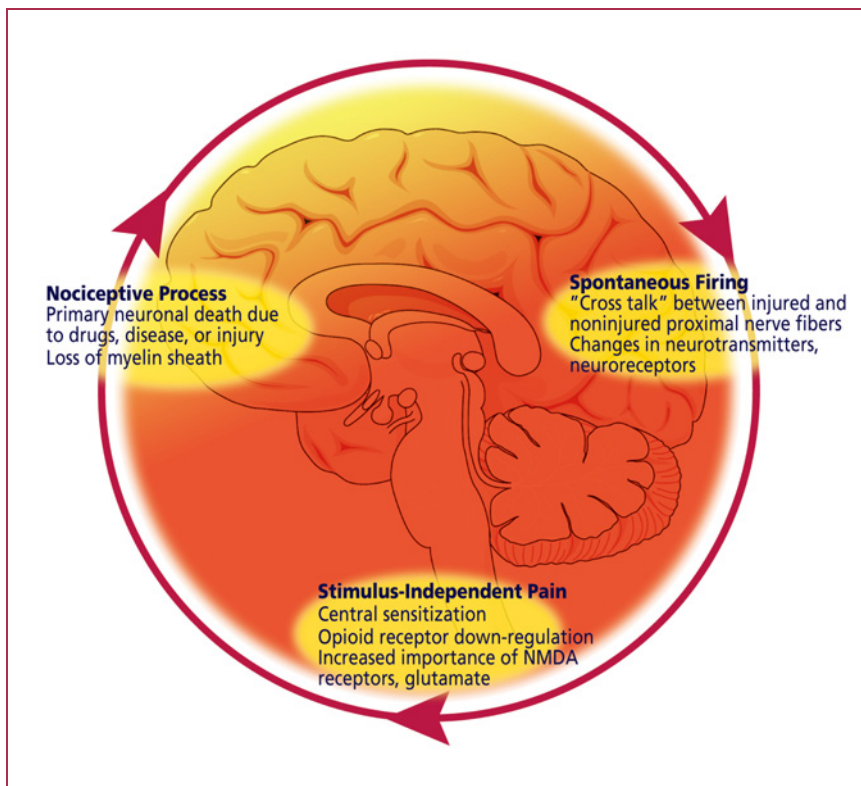


Figure 1. Complex neuropathic pain. (NMDA indicates N-methyl-D-aspartate.)

sign,” clinicians have been exposed to analog scales such as the Wong Baker faces scale for rating pain intensity. Recently, pain researchers have focused attention on the idea that accurate measurement of pain quality might provide insight into treatment effects too subtle to be noted when global measures are similar.<sup>13</sup> This accuracy is especially important for neuropathic pain, because specific sensory characteristics (such as burning or tingling) may spotlight pathophysiologic mechanisms of the pain and give clues to the type of intervention most likely to result in palliation.

Examples of standardized scales used for pain assessment include: the Short Form McGill Pain Questionnaire (SF-MPQ),<sup>14</sup> 100-mm visual analog scales (VAS),<sup>15</sup> numeric rating<sup>16</sup> and faces scales,<sup>17</sup> the Pain Disability Index,<sup>18</sup> the Pain Catastrophizing Scale (PCS),<sup>19</sup> and the Neuropathic Pain Scale (NPS).<sup>20</sup> These scales underscore the fact that it may be difficult for clinicians to assess or rate a patient’s pain because the level of perceived pain may be much greater than what is observable. Pain scales provide useful, standardized, and validated

tools for charting an individual’s response to a pain-control intervention.

### Treatment

Neuropathic pain tends to exhibit a relatively poor response to traditional analgesics.<sup>5,7</sup> No cure for neuropathy exists; however, palliation of pain, restoration of therapeutic sleep, maintenance of function, and improvement in overall quality of life remain the mainstays of treatment.

Adequate treatment trials demand a long-term commitment from both patient and physician.<sup>4</sup> For any regimen to be effective, both adherence to the prescribed agent and adequate time for the trial are needed. As with many difficult medical problems, a multidisciplinary approach to treatment is often the most successful. A multidisciplinary pain relief team includes primary care physicians, neurologists, pain specialists such as anesthesiologists or neurosurgeons, psychiatrists, psychologists, pastoral counselors, advanced practice nurses, clinical pharmacologists, and others. As always, the most important member of this team is the patient.

Medications used to treat neuro-

pathic pain include over-the-counter analgesics, anticonvulsants, tricyclic antidepressants (TCAs), topical anesthetic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), antiarrhythmics, narcotic analgesics, and opioids<sup>2,4,7</sup> (Figure 2). This varied armamentarium reflects the heterogeneity of the patient group and the different pathophysiologic mechanisms postulated to produce neuropathic pain.

Examples of the heterogeneity of presentation of neuropathic pain can be seen by the differences caused by DPN or PHN versus deafferentation pain due to MS or spinal cord injury. Patients with DPN tend to complain of burning, tingling pain in their distal extremities, especially foot and ankle pain, and of abdominal paresthesias, perhaps related to gastroparesis.<sup>9,21,22</sup> Patients with MS have classic electric shocklike neuropathic pain (eg, Lhermitte's sign), characteristic of demyelinating disease. Patients with MS have diffuse paresthesias, hypoesthesia, and other symptoms. Patients with SCI with incomplete myelopathy manifest pain akin to phantom limb pain: unpleasant sensations in regions of the body below the level of cord injury. Inspection of the painful site yields no evidence of inflammation or obvious injury. In fact, the injury occurred at the time of insult to the spinal cord. These pains may mystify physicians and can cause significant distress to patients. (See "Patient Perspectives on Pain" Sidebar.)

Recently, Hansson and Dickenson<sup>23</sup> noted that treatment of patients with neuropathy may be based on "shared commonalities despite multiple etiologies." They concluded their review by stating that because there is little information on drugs affecting specific pain symptoms and no clear rationale for their use, treatment trials are warranted.<sup>23</sup> This conclusion supports the use of empiricism in selection of a treatment regimen for neuropathic pain.

Numerous treatment algorithms list trials of common analgesics such as ibuprofen or acetaminophen, topical treatment such as capsaicin cream or lidocaine patches, TCAs or other antidepressants (eg, amitriptyline hydrochloride, desipramine hydrochloride), and



## Patient Perspectives on Pain

*In preparing to write this overview of neuropathic pain, the author initiated conversations with several of her patients to elicit descriptions of how their individual pain symptoms feel and how it has affected their lives. Their responses follow.*

### ■ From a 34-year-old man with T10 paraplegia:

"You know, you'd have to have a complete injury not to feel pain. Not all quads and paras have complete injuries; we do have pain. The worst pain kind of starts like a pressure, like from an overworked muscle. Then it progresses into a burning, like a heat you can't make stop. It gets to the point where—honestly, doc—you don't want to live anymore.

"You know, you get a few days of bad weather and the pain starts up, and you're stuck in bed 3 or 4 days, it's rough.

"I haven't had a full night's sleep since 1997. [Motor vehicle accident in 1997 caused spinal cord injury.]

"Don't forget to tell your readers that chronic pain destroys relationships. It can destroy friendships and social life. Friends call to ask me to go down the shore and sit on the beach; I can't do that! Fifteen minutes in the car and I have to turn around and go back so I can lie down." [Patient has symptoms of autonomic dysfunction, such as sweating and tachycardia, that are the cause.]

### ■ From a 53-year-old man with type 1 diabetes mellitus:

"The pain in my hands is so bad sometimes, it feels like my hands are stuffed too tightly into the skin and they are going to explode. It keeps me awake at night. And my feet don't feel like feet. Half the time they are numb blocks, and the other half they're burning.

"My family is going to Europe this summer, and I decided to stay home. I just can't sit that long on a plane without being in extreme pain.

"I guess you can tell that my mood is affected by this."

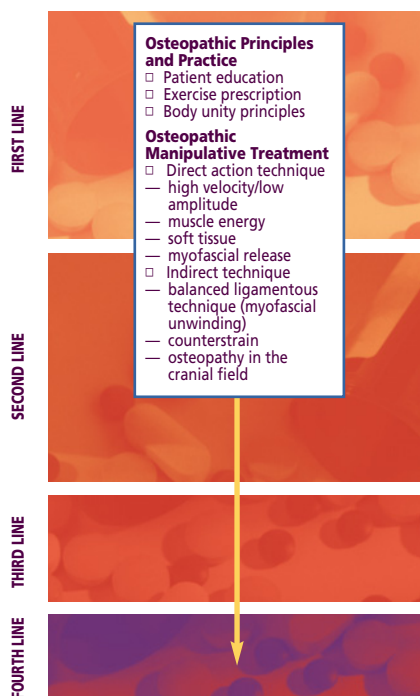
[Nonetheless, this patient refuses antidepressant therapy on the grounds that he already takes too many medications.]

### ■ From a 56-year-old woman with chronic progressive multiple sclerosis:

"I know you doctors try to help us, but you can't know how it feels. When I try to move sometimes, it's like someone is jabbing me with a hot poker. My muscles jump, and it feels like the nerves are being shocked. You know, this is just miserable.

"I hate to let my daughter see me when I'm in pain, because I look and feel like a witch. I think it scares her, and that's why she doesn't come to visit me very often. I miss being able to watch her grow up." [The patient has lived in a nursing facility for more than 10 years; she is wheelchair bound and unable to perform self-care.]

**Figure 2.** Treatment algorithm for neuropathic pain. (Modified to include osteopathic principles and practice and osteopathic manipulative treatment. From *Clinical Therapeutics, Vol 26*, Namaka M, Gramlich CR, Ruhlen D, Melanson M, Sutton I, Major J, A Treatment Algorithm for Neuropathic Pain, pp 951–979, Copyright 2004, with permission for print medium only from Excerpta Medica, Inc.)



anticonvulsants (eg, carbamazepine, gabapentin, lamotrigine) as first-line therapy for neuropathic pain.<sup>5,7,9</sup> These medications may be used alone or in combination. The choice of medication should be directed toward the type of painful symptom described.

Commonalities in presentation may influence the clinician's choice of pain medication. For example, PHN and DPN may produce spasms, burning, and tingling characteristic of neuronal hyperexcitability. Nervous system excitability can produce seizure activity. Thus, anticonvulsants are used with reasonable efficacy to treat patients with neuropathic pain.<sup>7,8</sup>

### Anticonvulsants

Neuropathic pain sufferers may respond to gabapentin, which is structurally related to  $\gamma$ -aminobutyric acid (GABA), a pain-modulating neurotransmitter. Gabapentin readily crosses the blood-brain barrier and has been studied for treatment of patients with DPN; pain relief efficacy was similar to that of TCAs except for a shorter onset of action. In a study of gabapentin as monotherapy, Backonja et al<sup>21</sup> noted that relatively high

doses were needed (3600 mg/d was the forced maximum dose, ie, the target maximum dose). Higher doses, however, limited upward titration because of side effects. The most common side effects were dizziness and somnolence, but weight gain, nausea, abdominal pain, asthenia, and other symptoms were also reported.

Other anticonvulsants have been used for both PHN and DPN; eg, patients with trigeminal neuralgia have been treated with carbamazepine for decades. A recent study of divalproex sodium for PHN noted subjective improvement in the treatment versus placebo group and found significant side effects in only one patient.<sup>24</sup> Trials of other anticonvulsants, eg, lamotrigine, may be indicated in patients with neuropathic pain refractory to alternatives.

### Topical Anesthetic Agents

Patients with PHN or other localized regions of peripheral neuropathy may respond well to topical lidocaine hydrochloride 5% patches, especially if the region of pain is relatively small and circumscribed. Studies demonstrated efficacy of topical lidocaine either as

monotherapy or in combination; it was safe, easily administered, and had minimal side effects.<sup>25,26</sup> Capsaicin cream has also been used effectively in patients with PHN but must be carefully applied because of its powerful irritating effects (which are related to the degree of subsequent analgesia).

### Antidepressants

Tricyclic antidepressants have been used for treatment of patients with DPN since the 1970s. These agents have documented pain-control efficacy<sup>27</sup> but are limited by a slow onset of action (analgesia in days to weeks), anticholinergic side effects (dry mouth, blurred vision, confusion/sedation, and urinary retention), and potential cardiac toxicity.

**Amitriptyline hydrochloride is the most extensively studied** of the TCAs, at oral doses of 10 mg to 25 mg at bedtime. This dose can be slowly titrated with escalating doses every 4 to 7 days. Frail and elderly patients may be unable to tolerate therapeutic doses because of sedation. Desipramine and nortriptyline are less-sedating alternatives to amitriptyline; plasma drug levels are available for the latter.

The advent of selective serotonin reuptake inhibitors (SSRIs) gave hope that they could be used for chronic pain without the concerns of cardiac toxicity and anticholinergic side effects. However, results have been disappointing. With the exception of duloxetine hydrochloride, **SSRIs are not indicated for neuropathic pain**; they may be useful adjuncts to treat patients who have pain with depression when TCAs are contraindicated. Duloxetine is a new SSRI which has received US Food and Drug Administration (FDA) approval for the PHN indication.

Patients with neuropathic pain are prone to depression, drug dependency, and insomnia. Interrupted sleep is one of the most difficult problems facing patients with neuropathy, as there is no way to escape the discomforting symptom. Antidepressants and sedative-hypnotic medications may be prescribed as important adjunctive therapy for neuropathy.

### **Antiarrhythmics**

Neuronal hyperexcitability resulting from nerve damage may respond to the effect of antiarrhythmic medications. A randomized trial of amitriptyline and mexiletine hydrochloride in a group of patients with painful distal sensory neuropathy due to HIV infection showed that dosages of amitriptyline hydrochloride up to 100 mg/d and mexiletine hydrochloride up to 60 mg/d were generally well tolerated.<sup>28</sup> However, this study's results failed to demonstrate significant pain relief for this indication.

### **Anti-inflammatory Agents**

The usefulness of NSAIDs such as aspirin and ibuprofen for neuropathic pain is limited. Use of NSAIDs for DPN should be discouraged because of the adverse effects of these drugs on renal function. The COX-2 inhibitors have been under scrutiny for adverse cardiovascular events and cannot be recommended for the long-term administration needed to treat patients with neuropathic pain syndromes.

### **Opioid Analgesics**

In response to severe or persistent pain, interneurons in the dorsal horn release

endogenous opioids that work to reduce perceived pain. These endogenous substances (enkephalins, endorphins, and dynorphins) play a major role in the mechanism of pain reduction and modulation by preventing transmission of pain signals to higher centers. Exogenously administered opioids mimic the effect of enkephalin and dynorphin at mu-type opioid receptors, which occur throughout the brain and spinal cord.<sup>6(pp207-228)</sup> This mechanism accounts for the efficacy of opioid analgesics in neuropathic pain syndromes.

**Tramadol** hydrochloride, a semi-synthetic opioid analgesic, may also affect neuropathic pain by **low-affinity binding to mu receptors as well as having weak inhibition of norepinephrine and serotonin reuptake, mirroring the mechanism of action of both opioids and TCAs**. One trial suggests that tramadol may be **better tolerated than TCAs** in some individuals with DPN or other neuropathic pain syndromes.<sup>29</sup>

Because of concerns about tolerance, abuse, and addiction, the use of opioids for nonmalignant pain was formerly considered controversial. In recent years, however, much research has supported the use of these agents. Opioids are now commonly and effectively used for treatment of neuropathic pain.<sup>7,22,27,30,31</sup>

A double-blind, dose-response study reported in 2003 used levorphanol tartrate (3 mg equivalent to 45 mg to 90 mg of oral morphine sulfate or 30 mg to 45 mg of oral oxycodone) and showed a 48% overall reduction in pain and moderate or better pain relief in 66% of patients.<sup>30</sup> The researchers noted that higher doses are more effective in reducing the intensity of chronic neuropathic pain. They also demonstrated that tolerance was not a clinically significant problem as only four patients in the high-strength group ever reached the maximal allowed dose. Further, they noted no addictive behavior.<sup>30</sup>

Raja et al<sup>27</sup> studied pain intensity, pain relief, cognitive and physical functioning, sleep, mood, side effects, and treatment preference in a group of patients with PHN. They compared responses to TCA therapy with those to opioids, noting that they both act via independent mechanisms and varied

individual effect. The study found that patients completing all three treatments (including placebo) preferred opioids to TCAs and concluded that opioids effectively treat patients with PHN without impairment of cognition.

### **NMDA-Receptor Antagonists**

**Nerve injury results in upregulation of NMDA receptors through repeated firing of peripheral afferent fibers and release of glutamate. This results in greater-than-expected peripheral pain.**<sup>6(pp207-228)</sup> NMDA-receptor blockers have been studied for their efficacy in chronic pain. **Currently available NMDA-receptor blockers include dextromethorphan hydrobromide, memantine hydrochloride, and ketamine.**<sup>10,32</sup>

NMDA receptors have been studied for their role in opioid tolerance. Adjunct use of ketamine may reduce morphine requirements and cause improvement in analgesia, as noted in case reports by Bell.<sup>33</sup> A larger study showed that **ketamine improves morphine analgesia in difficult pain syndromes (neuropathic pain caused by cancer)**; however, adverse effects on the central nervous system such as psychomimetic effects were noted.<sup>34</sup> The authors state that future studies must address treatments to prevent or reduce the central effects of ketamine.

### **Combined Analgesic Therapy**

Clinical experience supports the use of more than one agent for patients with refractory neuropathic pain. Because physiologic mechanisms causing pain may be several, use of more than one type of medication may be necessary. While monotherapy may be desirable, both for ease of administration and for reduction of potential side effects, this approach may not achieve satisfactory pain relief. The strategy of using two or more agents at lower doses to achieve synergistic pain efficacy has been proposed. Several studies have looked at two or more possible treatments as well as these agents in combination to assess the effectiveness of this strategy.<sup>27,28,35</sup>

Gilron et al<sup>35</sup> used a four-period crossover trial to assess the efficacy of morphine and gabapentin alone, these drugs in combination, and active placebo

(in the form of low-dose lorazepam). They concluded that the trial unequivocally showed that gabapentin significantly enhanced the efficacy of morphine and suggested that further studies of combination drug trials are warranted.

Osteopathic physicians are trained to treat the whole person, and, with this goal in mind, it must be remembered that side effects of medications may pose limitations to their use. Skillful and judicious use of adjuvants, here defined as any agent that enables the use of a primary medication to its full dose potential, is mandated. An obvious example of this practice is the customary use of laxatives in combination with opioids.

### Other Treatment Modalities

Osteopathic manipulative treatment (OMT) should be offered to all patients with neuropathic or other chronic pain syndromes as primary or adjunctive therapy, or both. Myofascial trigger point release for carpal or tarsal tunnel syndrome pain is an example of an effective primary technique. Indirect or passive myofascial techniques may be used to address all regions of tissue texture change. Adjunctively, educating patients with neuropathic pain about the importance of postural influence and functional movement can enhance their sense of well-being and maintain or improve physical functioning. Osteopathic exercise prescriptions should be given to assure that patients maintain active range of motion and ambulatory function.

As previously noted, drug treatment of patients with neuropathic pain lacks a standardized rationale and relies on clinical empiricism. Despite best efforts at treatment trials, some patients may continue to suffer. In these cases, referral to pain specialists is essential. Surgical interventions such as motor cortex stimulation,<sup>36</sup> transcutaneous electrical nerve stimulation (TENS) units, and other peripheral stimulation<sup>37</sup> have been shown to be helpful in these refractory cases.

### Prophylaxis

An important cause of neuropathic pain is herpes zoster ("shingles"), a condition caused by varicella-zoster virus reactivation decades after the initial episode of chickenpox. Shingles disproportionately

affects the population older than 60 years, the group likely to be contending with numerous other medical concerns. Unfortunately, the discomfort of shingles represents only the beginning of the problem for many patients who suffer for months or years from debilitating PHN.<sup>38</sup>

A large prospective, randomized, placebo-controlled, double-blind study was recently completed by the Shingles Prevention Study Group.<sup>38</sup> The study included 38,546 adults aged 60 years or older and used a highly potent zoster vaccine (several times the concentration of that used for primary vaccination against chickenpox in children). Vaccine recipients showed reduced burden of illness (incidence and severity) by greater than half (61.1%;  $P < .001$ ). The incidence of herpes zoster was reduced by 51.3%, and, most significantly, incidence of PHN was reduced by 66.5% ( $P < .001$ ). The authors suggest that the decreased morbidity due to PHN more than adequately offsets the cost of large-scale immunization of individuals aged 60 years or older.<sup>38</sup> The vaccine awaits FDA approval, and it remains to be seen whether the FDA will require further confirmatory trials for this promising vaccine.

### Comment

Relief from chronic pain has the potential to improve all aspects of a patient's life. Social and physical functioning, relationships, mood, sleep, overall health, and well-being are positively impacted by adequate control of debilitating pain symptoms. Osteopathic physicians are committed to treating the "whole person" and have the unique ability to diagnose and treat with their hands as well as with medications. The concept of working with other professionals and the patient to achieve pain control is congruent with the principles of osteopathic practice. It is specifically this type of treatment model that has the best chance for success in treating patients with neuropathic pain.

### References

1. Merskey H, Bogduk N, eds. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 2nd ed. Seattle, Wash: IASP Press; 1994.

2. Dworkin RH. An overview of neuropathic pain: syndromes, symptoms, signs, and several mechanisms. *Clin J Pain*. 2002;18:343-349.

3. Bennett GJ. Neuropathic pain: an overview. In: Borsook D, ed. *Molecular Neurobiology of Pain*. Seattle, Wash: IASP Press; 1997:109-113.

4. Bowsher D. The lifetime occurrence of herpes zoster and prevalence of postherpetic neuralgia: a retrospective survey in an elderly population. *Eur J Pain*. 1999;3:335-342.

5. Chen H, Lamer TJ, Rho RH, Marshall KA, Sitzman BT, Ghazi SM, et al. Contemporary management of neuropathic pain for the primary care physician. *Mayo Clin Proc*. 2004;79:1533-1545.

6. Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of Neural Science*. 4th ed. New York, NY: McGraw-Hill (Health Professions Division); 2000:175-186, 207-228.

7. Namaka M, Gramlich CR, Ruhlen D, Melanson M, Sutton I, Major J. A treatment algorithm for neuropathic pain. *Clin Ther*. 2004;26:951-979.

8. Ji R-R, Strichartz G. Cell Signaling and the Genesis of Neuropathic Pain. *Science's STKE*. 2004;252:1-19. Available at: <http://www.stke.science.mag.org/cgi/content/full/2004/252/re14>.

9. Spruce MC, Potter J, Coppini DV. The pathogenesis and management of painful diabetic neuropathy: a review. *Diabetic Medicine*. 2003;20:88-98.

10. Goldstein FJ. Adjuncts to opioid therapy. *J Am Osteopath Assoc*. 2002;102(9 suppl 3):S15-S20.

11. Devor M, Govrin-Lippmann R, Angelides K. Na<sup>+</sup> channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. *J Neuroscience*. 1993;13:76-92.

12. Boureau F, Doubrere JF, Luu M. Study of verbal description in neuropathic pain. *Pain*. 1990;42:145-52.

13. Jensen MP, Dworkin RH, Gammaitoni AR, Olaleye DO, Oleka N, Galer BS. Assessment of pain quality in chronic neuropathic and nociceptive pain clinical trials with the Neuropathic Pain Scale. *J Pain*. 2005;6:98-106.

14. Melzack R. The Short-Form McGill Pain Questionnaire. *Pain*. 1987;30:191-197.

15. Brown JA, Pilitsis JG. Motor cortex stimulation for central and neuropathic facial pain" a prospective study of 10 patients and observations of enhanced sensory and motor function during stimulation. *Neurosurgery*. 2005;56:290-297.

16. Hardy JD, Wolff HG, Goodell H. *Pain Sensations and Reactions*. Baltimore, Md: Williams & Wilkins; 1952.

17. Wong DL, Hockenberry-Eaton M, Wilson D, Winkelstein M, Schwartz P. *Whaley and Wong's Essentials of Pediatric Nursing*. 5th ed. St Louis, Mo: Mosby; 2001:1301.

18. Pollard CA. Preliminary validity study of the pain disability index. *Percept Mot Skills*. 1984;59:974.

19. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale. Development and Validation. *Psychological Assessment*. 1995;7(4):524.
20. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain; The Neuropathic Pain Scale. *Neurology*. 1997;48:332–338.
21. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280:1831–1836.
22. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology*. 2003;60:927–934.
23. Hansson PT, Dickenson AH. Pharmacological treatment of peripheral neuropathic pain conditions based on shared commonalities despite multiple etiologies. *Pain*. 2005;113:251–254.
24. Kochar DK, Garg P, Bumb RA, Kochar SK, Mehta RD, Beniwal R, et al. Divalproex sodium in the management of postherpetic neuralgia: a randomized double blind placebo-controlled study. *QJM*. 2005;98(1):29–34.
25. Katz NP, Gammaitoni AR, Davis MW, Dworkin RH, Lidoderm Patch Study Group. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. *Pain Med*. 2002;3:324–332.
26. Gammaitoni AR, Alvarez NA, Galer BS. Safety and tolerability of the lidocaine patch 5%, a targeted peripheral analgesic: a review of the literature. *J Clin Pharmacol*. 2003;43:111–117.
27. Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Trivison TG, Sabeen S, et al. Opioids versus antidepressants in postherpetic neuralgia: A randomized, placebo-controlled trial. *Neurology*. 2002;59:1015–1021.
28. Kiebertz K, Simpson D, Yiannoutsos D, Max MB, Hall CD, Ellis RJ, et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. *Neurology*. 1998;51:1682–1688.
29. Harati Y, Gooch C, Swenson M, Edelman SV, Greene D, Raskin P, et al. Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. *J Diabetes Complications*. 2000;14:65–70.
30. Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med*. 2003;348:1223–1232.
31. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112:372–380.
32. Sang CN, Booher S, Gilron I, Parada S, Max M. Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. *Anesthesiology*. 2002;96:1053–1061.
33. Bell RF. Low-dose subcutaneous ketamine infusion and morphine tolerance. *Pain*. 1999;83:101–103.
34. Mercadante S, Arcuri E, Tirelli W, Casuccio A. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy. *J Pain Symptom Manag*. 2000;20:246–252.
35. Gilron I, Bailey JM, Dongsheng Tu, Holden RR, Weaver DF, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;352:1324–1334.
36. Brown JA, Pilitsis JG. Motor cortex stimulation for central and neuropathic facial pain: a prospective study of 10 patients and observations of enhanced sensory Motor Function During Stimulation. *Neurosurgery*. 2005;56:290–297.
37. Johnson MD, Burchiel KJ. Peripheral stimulation for treatment of trigeminal postherpetic neuralgia and trigeminal posttraumatic neuropathic pain: a pilot study. *Neurosurgery*. 2004;55:135–142.
38. Oxman MN, Levin MJ, Johnson MS, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;352:2271–2284.

## About the JAOA's Pain Management Supplement Series Coordinating Editor

**Frederick J. Goldstein, PhD, FCP** brings expertise, experience, enthusiasm, and a dedicated interest in pain management to his role as coordinating editor of the current series of four JAOA supplements on pain management. A member of the JAOA's Editorial Advisory Board since 1998, Dr Goldstein is a professor of clinical pharmacology and coordinator of pharmacology in the Department of Neuroscience, Physiology and Pharmacology at the Philadelphia College of Osteopathic Medicine (PCOM). He is also a clinical research associate in the Department of Anesthesiology at Albert Einstein Medical Center in Philadelphia and a lecturer in pharmacology at the University of Pennsylvania School of Dental Medicine.

Dr Goldstein frequently lectures on drug abuse to community, social, and religious organizations and medical schools and staffs of medical centers.

Dr Goldstein has served as consultant to

the Philadelphia Field Office of the Drug Enforcement Administration, the Eastern District of the US Attorney's Office, and the Pennsylvania Board of Probation and Parole, among other agencies. He is a member of the editorial boards of the *Journal of Clinical Pharmacology* and the new *Journal of Opioid Management*. He is a reviewer for those publications as well as for the JAOA. Dr Goldstein is a Fellow of American College of Clinical Pharmacology, and his other societal memberships include the American Society for Pharmacology and Experimental Therapeutics, the International Association for the Study of Pain, and the American Pain Society.

In 1990, Dr Goldstein received the Lindback Award for Distinguished Teaching, Philadelphia College of Pharmacy and Science, now the University of the Sciences.

Dr Goldstein has no conflicts of interest to disclose.