Contemporary Management of Neuropathic Pain for the Primary Care Physician

HSIUPEI CHEN, MD; TIM J. LAMER, MD; RICHARD H. RHO, MD; KENNETH A. MARSHALL, MD; B. TODD SITZMAN, MD; SALIM M. GHAZI, MD; AND RANDALL P. BREWER, MD

Neuropathic pain (NP), caused by a primary lesion or dysfunction in the nervous system, affects approximately 4 million people in the United States each year. It is associated with many diseases, including diabetic peripheral neuropathy, postherpetic neuralgia, human immunodeficiency virus-related disorders, and chronic radiculopathy. Major pathophysiological mechanisms include peripheral sensitization, sympathetic activation, disinhibition, and central sensitization. Unlike most acute pain conditions, NP is extremely difficult to treat successfully with conventional analgesics. This article introduces a contemporary management approach, that is, one that incorporates nonpharmacological, pharmacological, and interventional strategies. Some nonpharmacological management strategies include patient education, physical rehabilitation, psychological techniques, and complementary medicine. Pharmacological strategies include the use of first-line agents that have been supported by randomized controlled trials. Finally, referral to a pain specialist may be indicated for additional assessment, interventional techniques, and rehabilitation. Integrating a comprehensive approach to NP gives the primary care physician and patient the greatest chance for success.


NERVOUS SYSTEM TRANSMISSION OF PAIN

The transmission of pain from the site of tissue injury is an important biological response that protects the organism from further injury. The transduction of pain involves the conversion of a noxious mechanical, inflammatory, or thermal stimulus into an electrical impulse. These electrical impulses arise within tissue nociceptors, sensory axons that are responsible for conducting pain signals into the dorsal horn of the spinal cord. Nociceptors, whose cell bodies are found in the dorsal root ganglia, transmit pain signals along thinly myelinated axons (A delta fibers) and unmyelinated axons (C fibers). Peripheral nociceptors, by release of the neurotransmitter glutamate, activate neurons that are responsible for the transmission of pain impulses centrally. These projection neurons (nociceptive neurons) cross the midline to form the contralateral spinothalamic tract. Axons of the projection neurons terminate in the somatosensory thalamus (ventral posterolateral and ventral posteromedial nuclei) and medial thalamus and provide collateral inputs to key brainstem nuclei such as the parabrachial pontine nucleus, the periaqueductal gray matter, and the reticular formation of brainstem.

Information regarding the location, quality, and intensity of pain is conveyed to the primary sensory cortex from the somatosensory thalamus. Projections from the medial thalamus and brainstem nuclei are responsible for limbic and autonomic activation through projections to the hypothalamus, insula, amygdala, and cingulate cortex. The cortical inputs culminate in the perception of a painful stimulus. Descending inhibitory pathways, predominantly...
located in the periaqueductal gray matter and dorsolateral fasciculus (Lissauer tract) of the spinal cord, are activated to modulate the transmission of nociceptive stimuli. Inhibition is achieved by release of endogenous opioids, norepinephrine, and serotonin in the dorsal horn, by recruitment of inhibitory interneurons that release the inhibitory neurotransmitter γ-aminobutyric acid (GABA), and by direct inhibition of pain projection neurons. Non-nociceptive, large-fiber input into the dorsal horn conveys information regarding pressure, light touch, and joint position sensation. These fibers, principally A beta fibers, branch into adjacent deeper layers of the dorsal horn and ascend as the ipsilateral dorsal column (fasciculus gracilis, fasciculus cuneatus) and contralateral medial lemniscus. These inputs also terminate in the ventrolateral somatosensory thalamus. Large-fiber inputs into the dorsal horn also may activate descending and local inhibitory mechanisms by activating local inhibitory interneurons through the release of GABA (Figure 1).

MECHANISMS OF NP

Neuropathic pain stems from neural dysfunction that persists beyond the period of normal tissue healing; therefore, long-lasting changes in the processing of sensory information by the nervous system are believed to underlie the presence of persistent pain. Both peripheral and central NP mechanisms have been identified in experimental models.

In some individuals, central sensitization results after a peripheral nerve injury induces changes in pain processing within the dorsal horn. It is characterized by hypersensitivity of dorsal horn neurons to both noxious and non-noxious input, a lowered threshold for activation, and expanded receptive fields. Sustained activation of nociceptors, such as that which occurs after peripheral nerve injury, leads to the activation of key excitatory amino acid receptors such as the N-methyl-D-aspartate (NMDA) receptor (Figure 2, A). Persistent nociceptor activation signals protein kinases and phosphorylation of the NMDA receptor, which results in intracellular calcium accumulation. Long-lasting changes in neuronal membrane excitability through the transcription of key gene products may be further induced and lead to long-lasting changes in the excitability of dorsal horn neurons. Other phenotypic changes in nociceptive neurons have been shown in experimental models, such as the recruitment of A beta fiber terminals into the superficial dorsal horn resulting in the aberrant A beta fiber activation of nociceptive neurons. Although a key target for new therapies has been the NMDA receptor, clinical trials of the efficacy and tolerability of the currently available NMDA antagonists have been disappointing.

Lesions of the dorsal horn of the spinal cord, spinothalamic tract, thalamus, and/or cerebral cortex (somatosensory and limbic cortex) may result in NP in patients with central pain. Reduced activation of key brainstem descending inhibitory systems normally modulated through endogenous opioid, serotonin, and norepinephrine pathways may result in neuropathic central pain (disinhibition). Disinhibition also may result from loss of inhibitory inputs into the dorsal horn (Figure 2, B). Treatments believed to act by restoring endogenous inhibitory systems include drugs that mimic descending or local inhibitory pathways (clonidine, tricyclic antidepressants [TCAs], opioids, GABA agonists) and nonpharmacological techniques such as transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), acupuncture, massage, and therapeutic exercise. Despite the widespread use of TENS units, evidence from randomized controlled trials is insufficient to show the efficacy of TENS in treating chronic pain. Cognitive-behavioral interventions may contribute to central inhibitory systems. In sympathetic activation, sympathetic nerve endings sprouting from a nearby blood vessel toward the site of injury can enhance signal transmission in the dorsal root ganglion. Catecholamine release and up-regulation of adrenergic receptors on free nerve endings and neuromas also contribute to sympathetically mediated pain (Figure 2, C).

Injury to peripheral nerves may lead to the phenomenon known as peripheral sensitization. Peripheral sensitization involves the hyperexcitability of peripheral nerve terminals, or nociceptors, normally responsible for the transduction of painful stimuli. Inflammatory mediators released as a result of tissue or nerve injury may induce spontaneous activity and hypersensitivity to mechanical stimuli in peripheral nociceptors. This may be a result of altered expression of sodium channels, calcium channels, and adrenergic receptors in peripheral nerves and dorsal root ganglia. These changes form the rationale for many of the drugs currently used in the treatment of peripheral NP (Figure 2, D).

CLINICAL MANIFESTATIONS OF NP

The hallmark of NP is the experience of both paresthesias (nonpainful abnormal sensations) and dysesthesias (unpleasant abnormal sensations). Spontaneous pain qualities such as burning, tingling, itching, and aching often coexist with evoked pain qualities such as shooting, stabbing, or electric pains. Hyperalgesia is an exaggerated response to a painful stimulus, whereas allodynia, pain after an innocuous stimulus, is common and often disabling. Hypoesthesia or anesthesia (reduction or loss, respectively, of normal sensation) in an area of NP is known as anesthesia dolorosa. Symptoms of NP from various etiologies are...
CONTEMPORARY MANAGEMENT OF NEUROPATHIC PAIN

FIGURE 1. Normal sensory tracts. The spinothalamic tract transmits input encoded for pain and temperature, and the dorsal column transmits input encoded for light touch. The free nerve ending of an A delta fiber or a C fiber senses pain and temperature and has its cell body in the dorsal root ganglion. This synapses in the dorsal horn with a second-order neuron that immediately crosses the midline and ascends on the contralateral side in the spinothalamic tract. The axons of the second-order neuron terminate in the hypothalamus and thalamus. In the thalamus, some projections are made directly to the primary sensory cortex, whereas others go to the limbic system, which includes the insula, amygdala, and cingulate cortex. The Pacinian corpuscle is a first-order neuron that senses pressure. This neuron's cell body is also in the dorsal horn, and the axon ascends a few levels, crosses the midline, and ascends in the contralateral dorsal column/medial lemniscus, through the medulla and midbrain, and terminates in the thalamus. There, the neuron synapses with a second-order neuron, which projects to the primary sensory cortex.
### Mechanisms of Neuropathic Pain

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Therapeutic options</th>
</tr>
</thead>
</table>
| **A. Central sensitization** | - Ca²⁺ channel antagonists  
- NMDA receptor antagonists  
- Glutamate antagonists |
| **B. Reduced inhibition** | - Central α-receptor agonists  
- NE reuptake inhibition  
- Serotonin reuptake inhibition  
- GABA agonists  
- TENS  
- SCS  
- Opioids |
| **C. Sympathetic activation** | - Central α-receptor agonists  
- Peripheral α-receptor antagonists  
- Sympathetic nerve blocks  
- Systemic sympatholytics |
| **D. Peripheral sensitization** | - Na⁺ channel antagonists  
- Ca²⁺ channel antagonists |

**FIGURE 2.** Mechanisms of neuropathic pain and therapeutic options. Mechanisms (left column): A, Central sensitization. Overactivity of a second-order neuron in the dorsal horn leads to enhanced pain transmission. In some individuals, central sensitization results after a peripheral nerve injury induces changes in pain processing within the dorsal horn. It is characterized by a lowered threshold for activation and expanded receptive fields, leading to the activation of key excitatory amino acid receptors such as the N-methyl-D-aspartate (NMDA) receptor. B, Disinhibition. Reduced activation of key central inhibitory inputs from the dorsolateral fasciculus (purple) through endogenous opioid, serotonin, and norepinephrine pathways may result in neuropathic central pain (left). Disinhibition also may result from loss of local inhibitory pathways from an interneuron (right). C, Sympathetic activation. Sympathetic nerve endings sprout from a nearby blood vessel toward the site of injury and can enhance signal transmission in the dorsal root ganglion. Catecholamine release and up-regulation of adrenergic receptors on free nerve endings and neuromas also contribute to sympathetically mediated pain. D, Peripheral sensitization. Injury to peripheral nerves may lead to the hyperexcitability of peripheral nerve terminals, or nociceptors, normally responsible for the transduction of painful stimuli. This may be a result of altered expression of sodium channels, calcium channels, and adrenergic receptors in peripheral nerves and dorsal root ganglia. Therapeutic options (right column): Therapeutic options for modulating the transmission of neuropathic pain are shown adjacent to each of the 4 mechanisms. GABA = γ-aminobutyric acid; NE = norepinephrine; SCS = spinal cord stimulation; TENS = transcutaneous electrical nerve stimulation.
remarkably similar (eg, 2 individuals with postherpetic neuralgia [PHN] and diabetic peripheral neuropathy [DPN] may both experience burning pain). These observations have led to a shared-mechanism concept for the evaluation of NP pathophysiology and prospective treatments.3

EPIDEMIOLOGY AND ETIOLOGIES OF COMMON NP DISORDERS

Neuropathic pain affects nearly 4 million people in the United States.19 Disorders of the brain or spinal cord can lead to “central pain,” such as that encountered in multiple sclerosis, after a stroke, and in spondylotic and posttraumatic myelopathy. Peripheral nervous system disorders include diseases of the spinal nerve roots, dorsal root ganglia, and peripheral nerves. Focal lesions of the peripheral nervous system that occur, for example, after amputation and with radiculopathy, carpal tunnel syndrome, and other entrapment neuropathies are usually distinguishable from diffuse disorders such as diabetic polyneuropathy, human immunodeficiency virus (HIV) sensory neuropathy, and idiopathic small-fiber sensory neuropathy.

Diabetic peripheral neuropathy occurs in persons with diabetes at a rate of 11.6% in those who are insulin dependent and 32.1% in those who are not, with an estimated prevalence of up to 3 million persons in the United States.20,21 The most common form of painful DPN causes spontaneous burning pain, numbness, and allodynia in the lower extremities. There may be concomitant carpal tunnel syndrome or meralgia paresthetica, pain in the distribution of the lateral femoral cutaneous nerve. Loss of small-fiber sensation in the stocking-glove distribution usually is present in patients with diabetes who have pain. Nocturnally exacerbated symptoms are extremely common; they may prevent restorative sleep and lead to secondary fatigue, irritability, and myofascial dysfunction. Glycemic control currently is emphasized to delay onset and progression of DPN.22

In the United States, 600,000 to 800,000 cases of herpes zoster occur each year, and between 9% and 24% of these patients will develop PHN.21,23 After acute herpes zoster infection, PHN develops in 50% of persons older than 70 years and may lead to disability, depression, and social isolation. Frequently, background burning or aching pain is accompanied by paroxysmal stabbing or itching and severe, evoked allodynia and hyperalgesia.17,18 Fields et al16 showed that both peripheral and central mechanisms are responsible for the variable manifestations of PHN. Promising strategies for prevention of PHN pain include early treatment with agents specific for NP, antiviral medications, and varicella zoster alloimmunization.24

Low back and neck pain are among the most common reasons for physician visits.25 Although the percentage of patients with low back and neck pain of solely NP origin is unknown, chronic radicular pain develops in more than 20% of those requiring spinal surgery, with an annual prevalence of more than 2 million cases in the United States.1,19 In addition to axial pain, patients with chronic radiculopathy usually experience activity-dependentaching, burning, and lancinating or stabbing pain in the sensory distribution of a nerve root. Occasionally, spontaneous burning or lancinating pain predominates, especially in patients with other evidence of neurologic dysfunction such as sensory loss, weakness, and/or loss of deep tendon reflexes. The degree of reported pain intensity or disability may not correlate with the physical examination or radiographic findings. Superimposed myofascial, inflammatory, and skeletal nociceptive pain generators often coexist. These factors, combined with physical deconditioning, psychological comorbidity, and third-party involvement (eg, disability claims, litigation) contribute to the complexity of rehabilitation. Unfortunately, in the setting of acute low back and neck pain, few treatments have been evaluated adequately for their ability to prevent the chronic condition or limit nerve injury. Opportunities for prevention of long-term disability may include early mobilization and physical therapy facilitated by aggressive symptomatic management, patient education, and psychological interventions in high-risk patients. Pharmacotherapy alone is rarely effective, and interdisciplinary management strategies may be required.

The complex regional pain syndrome (CRPS) has been estimated to be present in 100,000 persons in the United States.19 Formerly known as reflex sympathetic dystrophy, CRPS type I is characterized by the development of NP after tissue trauma such as surgery or bone fracture. In CRPS type II, formerly known as causalgia, NP results from an injury to a peripheral nerve with pain that extends beyond the distribution of the injured nerve.1 In both types, hallmark features of CRPS such as asymmetric sweating, changes in skin texture, diminished skin temperature, and fluctuating degrees of swelling may accompany more universal symptoms of NP such as burning, allodynia, and motor dysfunction. By definition, these symptoms outlast the period of normal tissue healing. Results of electrodiagnostic studies (eg, electromyography, nerve conduction studies), autonomic testing, and 3-phase radionuclide bone scan may support the diagnosis and assist with the exclusion of other conditions. Neuropathic pain in CRPS is considered sympathetically maintained when it is reduced by sympatholytics or sympathetic nerve blocks. Sympathetic-independent pain may emerge in the later stages of the illness.26
An uncommon condition, idiopathic trigeminal neuralgia (TN) is characterized by paroxysmal, lancinating, and evoked pain in the distribution of 1 or more divisions of the trigeminal nerve. Patients who have sensory loss or other neurologic symptoms need to be evaluated for a primary nervous system structural lesion or an inflammatory disorder such as multiple sclerosis. The symptoms of TN can be debilitating. For example, speaking or chewing may become incapacitating. Treatment of TN differs from that of other neuropathic disorders because many patients with TN are sensitive to carbamazepine. Second-line alternatives include oxcarbazepine, lamotrigine, baclofen, clonazepam, and phenytoin. In refractory TN, referral to a pain specialist or a neurosurgeon is indicated for consideration of other management strategies. These include gasserian ganglion glycerol neurolysis, trigeminal balloon decompression, microvascular decompression, or gasserian ganglion lesioning with gamma knife or radiofrequency technology.27

Neuropathic pain is a common and important source of morbidity in patients with cancer. Neuropathic symptoms often coexist with nociceptive pain generators such as bone metastases and visceral pain. The most common cancer-related etiologies of NP include tumor-related neural compression, radiation-induced neural injuries, and neuropathies related to paraneoplastic disorders and chemotherapeutic agents.28 Although the mainstay of pharmacological treatment of cancer-related pain is opioids, referral to a pain management center for neurolytic blocks or other medical management strategies. These include gasserian ganglion glycerol neurolysis, trigeminal balloon decompression, microvascular decompression, or gasserian ganglion lesioning with gamma knife or radiofrequency technology.27

Antidepressants commonly are prescribed for NP. Their efficacy is not related simply to the treatment of coincident depression. Possible mechanisms include sodium channel blockade and the facilitation of endogenous inhibition of pain.31 Evidence suggests that agents with adrenergic or mixed serotonergic and adrenergic mechanisms, such as TCAs, are generally more efficacious than selective serotonin reuptake inhibitors.32,33

The primary amine subclass of TCAs has been studied most, particularly amitriptyline. Inhibition of H1-histaminergic, α1-adrenergic, and muscarinic cholinergic receptors accounts for most of the adverse effects, the most serious of which are cardiac conduction disturbances, orthostatic hypotension in the elderly population, agranulocytosis, thrombocytopenia, and precipitation of acute angle-closure glaucoma.34 The TCAs are more lethal in overdose than other antidepressants, an important consideration in patients with comorbid depression. Generally preferred over the tertiary amines, the secondary amines (eg, nortriptyline, desipramine) tend to have fewer adverse effects with similar efficacy.35

In general, the tricyclics are initiated at low doses (Table 1) and are slowly increased every 3 to 7 days until the patient experiences acceptable relief or develops unmanageable adverse effects. Individual variability and the presence of comorbid conditions dictate careful titration in each patient. Serum drug levels are indicated when the dosage exceeds approximately 100 mg daily and if pain relief or intolerable adverse effects have not occurred. Common adverse effects such as dry mouth, somnolence, constipation, increased appetite, and urinary retention should be reviewed carefully with the patient; close monitoring during titration reinforces compliance and early feedback about adverse effects. Nightly dosing may be desirable in

PHARMACOLOGICAL OPTIONS FOR TREATING NP

Unfortunately, advanced understanding of NP mechanisms has not led to the ideal of mechanism-based treatment. In most cases, correlation of specific mechanisms with examination findings is difficult. For example, allodynia may result from either peripheral or central mechanisms. Also, it may be challenging for the clinician to distinguish neuropathic from nociceptive pain. Further elucidation of cognitive and behavioral dimensions of a patient’s pain is another important step toward individualizing therapy.

On the basis of current evidence from randomized clinical trials, recommendations for first-line pharmacotherapy for NP have been established. First-line agents for treatment of NP include TCAs, gabapentin, topical lidocaine, tramadol, and opioids. When choosing a first-line agent, the clinician should consider the weighted efficacy of each agent, the adverse effects, the neuropathic disorder, and any comorbidities.3 The most commonly used pharmacological options are summarized in Table 1.

ANTIDEPRESSANTS

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### TABLE 1. Commonly Used Medications for Treating Neuropathic Pain*

<table>
<thead>
<tr>
<th>Pharmacological mechanism(s)</th>
<th>Drug (class)</th>
<th>Starting†</th>
<th>Maintenance†</th>
<th>Frequency</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na channel blockade</td>
<td>Topical lidocaine (5%) (local anesthetic)</td>
<td>1-4 patches</td>
<td>1-4 patches</td>
<td>12 h on, 12 h off</td>
<td>Erythema, local pruritus</td>
</tr>
<tr>
<td>Serotonin, norepinephrine reuptake inhibition, Na channel blockade</td>
<td>Amitriptyline (antidepressant–tertiary amine tricyclic)</td>
<td>10-25</td>
<td>50-150</td>
<td>Once daily at nighttime</td>
<td>Orthostasis, xerostomia, urinary retention, blurry vision, sedation, constipation, weight gain</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline (antidepressant–secondary amine tricyclic)</td>
<td>10-25</td>
<td>50-100</td>
<td>Once daily at nighttime</td>
<td>Orthostasis, xerostomia, urinary retention, blurry vision, anxiety, constipation, weight gain, sedation; less severe than with tertiary amines</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibition</td>
<td>Paroxetine (antidepressant)</td>
<td>10-20</td>
<td>20-80</td>
<td>Once daily in the morning</td>
<td>Headache, sweating, insomnia, nausea, sedation, sexual dysfunction</td>
</tr>
<tr>
<td></td>
<td>Citalopram (antidepressant)</td>
<td>10-20</td>
<td>20-80</td>
<td>Once daily in the morning</td>
<td>Headache, sweating, insomnia, nausea, sedation, sexual dysfunction</td>
</tr>
<tr>
<td>Serotonin, norepinephrine reuptake inhibition</td>
<td>Duloxetine (antidepressant)</td>
<td>20-30</td>
<td>60</td>
<td>Once or twice daily</td>
<td>Nausea, somnolence, dizziness, constipation, dry mouth, sweating, decreased appetite</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibition</td>
<td>Venlafaxine (antidepressant)</td>
<td>37.5-50.0</td>
<td>150-300</td>
<td>Once daily in the morning</td>
<td>Insomnia, sweating, sexual dysfunction, headache, anorexia, hypertension</td>
</tr>
<tr>
<td>Dopamine, norepinephrine reuptake inhibition</td>
<td>Bupropion (antidepressant)</td>
<td>50-100</td>
<td>200-400</td>
<td>Once daily in the morning</td>
<td>Ataxia, nausea, fatigue, dizziness, somnolence, peripheral edema</td>
</tr>
<tr>
<td>Calcium channel (α2δ subunit) antagonism</td>
<td>Gabapentin (antiepileptic)</td>
<td>100-300</td>
<td>900-3600</td>
<td>3 times daily</td>
<td>Rash, sedation, ataxia, diplopia, nausea, vomiting, leukopenia, aplastic anemia (rare), hyponatremia (rare)</td>
</tr>
<tr>
<td>Na channel blockade</td>
<td>Carbamazepine (antiepileptic)</td>
<td>100-200</td>
<td>600-1200</td>
<td>Twice daily</td>
<td>Rash, ataxia, blurred vision, diplopia, headache, nausea, vomiting, Stevens-Johnson syndrome (rare)</td>
</tr>
<tr>
<td>Na channel blockade, glutamate release inhibition</td>
<td>Lamotrigine (antiepileptic)</td>
<td>25-50</td>
<td>300-500</td>
<td>Twice daily</td>
<td>Rash, ataxia, blurred vision, diplopia, headache, nausea, vomiting, Stevens-Johnson syndrome (rare)</td>
</tr>
<tr>
<td>Calcium channel (α2δ subunit) antagonism</td>
<td>Pregabalin (antiepileptic)</td>
<td>50-100</td>
<td>150-600</td>
<td>3 times daily</td>
<td>Dizziness, somnolence, peripheral edema, blurry vision, xerostomia</td>
</tr>
<tr>
<td>Opioid µ-receptor agonist</td>
<td>Oxycodone (semisynthetic opioid)</td>
<td>5-10</td>
<td>20-160</td>
<td>Every 4 to 6 h; twice daily if ER</td>
<td>Sedation, nausea, vomiting, pruritus, constipation, dysphoria</td>
</tr>
<tr>
<td></td>
<td>Morphine (opioid)</td>
<td>15-30</td>
<td>30-300</td>
<td>Every 4 to 6 h; 1-3 times daily if ER</td>
<td>Sedation, nausea, vomiting, pruritus, constipation, dysphoria</td>
</tr>
<tr>
<td></td>
<td>Transdermal fentanyl (synthetic opioid)</td>
<td>25 μg/h patch</td>
<td>25-150 μg/h patch</td>
<td>Every 48-72 h</td>
<td>Sedation, nausea, vomiting, pruritus, constipation, dysphoria</td>
</tr>
<tr>
<td>Opioid µ-receptor agonist (isomer l-methadone), NMDA receptor antagonism (isomer δ-methadone)</td>
<td>Methadone (synthetic opioid)</td>
<td>5-10</td>
<td>20-80</td>
<td>1-4 times daily</td>
<td>Dysphoria, sedation, nausea, vomiting, constipation, drug accumulation, respiratory depression</td>
</tr>
<tr>
<td>Nonopioid µ-receptor agonist, serotonin, norepinephrine reuptake inhibition</td>
<td>Tramadol (synthetic µ-receptor agonist)</td>
<td>37.5-50.0</td>
<td>200-400</td>
<td>Every 6-8 h</td>
<td>Sedation, seizures, constipation, confusion (in the elderly population)</td>
</tr>
</tbody>
</table>

*ER = extended-release formulation; NMDA = N-methyl-D-aspartate.†Units are mg/d unless stated otherwise.

Patients with nocturnal pain and insomnia. Minor adverse effects can be treated symptomatically (eg, with use of sialagogues, stool softeners, changes in timing of administration). Inadequate trials are common because of poor management of adverse effects, early discontinuation (trials should last 6-8 weeks), and insufficient dosing.35,36

The selective serotonin reuptake inhibitors citalopram and paroxetine have been shown to be superior to placebo in trials of DPN; however, clinical experience suggests their effects are weak.33,37 One randomized trial has suggested use of the antidepressant bupropion, a dopaminergic, norepinephrine reuptake inhibitor, for treatment of
NP.38 Bupropion has the added benefit of aiding in smoking cessation and is generally non-sedating, both commonly desired effects in many patients with chronic pain. Newer antidepressants such as venlafaxine inhibit norepinephrine and serotonin reuptake without the adverse effects of TCAs. A recent study suggests the efficacy of venlafaxine is similar to that of the TCA imipramine in treatment of NP associated with painful polyneuropathy.39 Duloxetine, a potent serotonin and norepinephrine reuptake inhibitor recently approved by the Food and Drug Administration, has been shown to be efficacious in treating pain caused by DPN at doses of 60 mg and 120 mg daily.40

**Antiepileptics**

Antiepileptics modulate both peripheral and central mechanisms via sodium channel antagonism, inhibition of excitatory transmission (eg, NMDA receptor), or enhancement of GABA-mediated inhibition. Most antiepileptics have multiple potential modes of action that may be beneficial for NP. Individual variability occurs; even among drugs with similar principal mechanisms, some patients may respond preferentially to a certain drug. Current studies suggest equal efficacy and tolerability with the use of antidepressants or antiepileptics in the treatment of NP.41 Gabapentin is recognized widely as an effective agent in the treatment of NP. Although its exact mechanism of action is unknown, it antagonizes voltage-gated calcium channels in afferent neurons and modulates central nervous system GABA activity.42 Trials in DPN and PHN have shown its efficacy, similar to that noted with amitriptyline.43-45 Most patients tolerate a starting dosage of 300 mg nightly, with increases every 3 to 7 days to 300 mg twice daily and then 300 mg 3 times per day. Titration is continued in 300-mg increments until the patient experiences acceptable relief, intolerable adverse effects, or lack of effect despite a total dose of 3600 mg daily. Temporary suspension of dose escalation may allow tolerance of adverse effects to develop. A recent study reinforced the fact that a total dose of 1800 to 3600 mg per day of gabapentin is well tolerated by most patients.46 Elderly patients and patients sensitive to the drug should initially receive 100 mg at night with weekly increases of 100 mg. The most common adverse effects are sedation, fatigue, nausea, and incoordination. Currently awaiting Food and Drug Administration approval, pregabalin (isobutyl-GABA) inhibits ectopic discharges from injured nerves, inhibits voltage-gated calcium channels (α, δ subunit), and has shown efficacy in PHN.47

Phenytoin suppresses ectopic discharges by inhibition of voltage-gated sodium channels and suppression of glutamate release.48 It is useful as a second-line agent in patients with TN, but data in other disorders are conflicting.31,41,49 The need for serum monitoring, incidence of adverse effects, and availability of newer agents have decreased use of phenytoin.

Carbamazepine, structurally related to TCAs, has a mode of action similar to that of phenytoin. Trials in patients with TN, DPN, and PHN have shown efficacy over placebo.50,51 Serious adverse effects such as leukopenia, aplastic anemia, and hyponatremia may develop during initiation of therapy. Routine serum monitoring of electrolytes and hematologic indexes should be conducted at baseline and periodically throughout treatment. Patients with an elevated risk of leukopenia (low or borderline pretreatment white blood cell counts) should be monitored regularly during the first 3 months of therapy.52 A carbamazepine analogue, oxcarbazepine, does not yield the epoxide metabolite that contributes to the drug interaction and adverse-effect profile of carbamazepine.53 Oxcarbazepine has shown similar effects as carbamazepine against mechanical hyperalgesia and allodynia in experimental models and may be effective in carbamazepine-responsive patients with poor tolerance.54 There is evidence for the efficacy of oxcarbazepine in treating PHN and DPN55; in 1 controlled trial, it was efficacious in treating DPN at a mean dose of 814 mg/d, and the most commonly experienced adverse effects were drowsiness and dizziness.56 Lamotrigine works as a sodium channel inhibitor and inhibits glutamate release. Recent trials have shown efficacy in central pain, HIV-related NP, and DPN. Lamotrigine has a risk of serious rash and Stevens-Johnson syndrome, especially with rapid titration.57,58 Although evidence from large-scale, randomized clinical trials is lacking, anecdotal reports suggest that the antiepileptic drugs topiramate, zonisamide, levetiracetam, valproate, and tiagabine may be useful solely in selected patients or as additions to first-line agents.40,58

**Opioids**

Randomized controlled trials have shown the efficacy of opioids in treating NP.59 Studies have shown oxycodone to be effective in treating PHN and DPN, with efficacy and tolerability comparable to TCAs and gabapentin.59,60 Low-dose methadone has been shown effective in improving the visual analog scale ratings of patients with NP of mixed etiologies.61 High-dose opioid therapy with the µ-receptor agonist levorphanol showed improved efficacy over low-dose therapy in reducing NP at the expense of increased adverse effects and treatment-related study withdrawals.62 Opioids appear to block A delta fiber- and C fiber-mediated pain but may be less likely to reduce A beta fiber-mediated mechanical allodynia. Additionally, methadone and propoxyphene antagonize the NMDA receptor. This property may be of benefit in opioid tolerance and central
other opioids. The unique pharmacokinetic and pharmacodynamic profile of methadone requires careful consideration during dose titration and conversion from other opioids. 

Tramadol, a centrally acting, weak opioid µ-receptor agonist, also weakly inhibits norepinephrine and serotonin reuptake and promotes serotonin release. Its effectiveness in treating NP has been shown in patients with DPN and polyneuropathy. 

Tramadol may precipitate seizures at higher doses and interact with other drugs with serotonin reuptake inhibition, such as TCAs.

Benefits from long-term opioid therapy must be weighed against the possible occurrence of opioid-induced hyperalgesia, opioid tolerance (the need to increase the dose to maintain an effect), and the potential for abuse. Aberrant drug-seeking behavior may signal addiction, opioid diversion, or undertreatment. Empirical evidence suggests that the incidence of addiction in the population with chronic pain is extremely low or at least similar to that of the normal population (approximately 6%). Nevertheless, physiologic dependence may occur with prolonged use. Patients must be warned not to discontinue opioids abruptly or without supervision. Patients with a recent history of substance abuse usually require the assistance of pain specialists and addictionologists. Individual responsiveness to opioids can vary substantially; therefore, care must be taken to ensure that the titration is done safely and that treatment goals are set and maintained. Transfer of care back to the primary care physician after a suitable medication regimen has been established allows for coordination of care.

The adverse effects of opioid use are well known but often manageable. Common, troublesome adverse effects include constipation, cognitive dysfunction, and nausea. Less frequent are pruritus, urinary hesitancy, and anorexia. Constipation prophylaxis should be initiated at outset of opioid therapy. Bulk agents, increased dietary fiber, and generous fluid intake are often sufficient. Stool softeners and laxatives sometimes are needed. Tolerance to sedation occurs usually within several weeks. If sedation persists, judicious use of methylphenidate or modafinil (psycho-stimulants) can be effective.

The efficacy and risks associated with long-term opioid therapy have not been elucidated fully in NP. Notably, long-term opioid doses greater than 300-mg oral morphine equivalents per day have not undergone extensive longitudinal study. The important clinical issues of opioid-induced hyperalgesia, immunosuppression, and effects on endocrine function have tempered enthusiasm for the “no ceiling” paradigm for opioid dosing in chronic pain. 

Guidelines regarding use of opioids in the management of chronic nonmalignant pain have been published. Persistent, intolerable adverse effects in opioid-responsive patients may warrant consideration of intrathecal opioid therapy.

**OTHER AGENTS**

Baclofen, a GABA-B receptor agonist used primarily as an antispasticity agent, has been used effectively in patients with TN and may be effective in other disorders. Sedation, hypotonia, and confusion in elderly persons may complicate therapy. Effective in the treatment of dystonia associated with CRPS and refractory spasticity, intrathecal baclofen has produced anecdotal evidence as an adjuvant treatment of NP.

Clonidine, an α₂-adrenergic receptor agonist, may be an effective analgesic in some patients. Neuraxial clonidine has been shown effective in treatment of NP associated with cancer and may be better tolerated than systemic administration. It appears to work by mimicking the effects of endogenous pain-inhibiting monoaminergic neurotransmitters (eg, norepinephrine). However, its long-term efficacy in NP not associated with cancer will require validation. The reported analgesic benefit of tizanidine, another α₂-adrenergic agonist and antispasticity agent, awaits confirmation.

Sodium channel blockers (intravenous lidocaine and mexiletine) and NMDA antagonists (dextromethorphan and ketamine) may benefit selected, refractory syndromes. Because of the narrow therapeutic indexes of these agents, they are usually initiated by pain management specialists.

Topical agents have limited potential for systemic toxicity and drug interactions. Effective in PHN, topical lidocaine is considered a first-line therapy in NP. Topical lidocaine also has been shown effective in DPN. Serum lidocaine levels are well below those observed during systemic infusions, with limited drug interactions. Capsaicin, the active ingredient in chili peppers, opens a heat-activated ion channel (vanilloid receptor subtype 1) modulating substance P in peripheral axon terminals. It is occasionally effective in patients who tolerate its initial burning effects.

**CONTEMPORARY PRINCIPLES OF PAIN MANAGEMENT**

Initial evaluation by the primary care physician entails detailed review of the diagnosis and previous treatments. Patients need reassurance that disease-based treatments are optimized. Educating patients about pain mechanisms diminishes their fears of undiagnosed disease. Patients should understand that complete relief may not occur and be reassured of the clinician’s commitment to helping them...
best tolerate their pain. Coexistent physical deconditioning, insomnia, and psychological comorbidity require directed approaches and periodic reassessment.

**Assessment and Evaluation**

The primary care physician should first assess the nature of the patient’s pain. Individual pain assessment remains primarily subjective. The visual analog scale and numeric rating scales allow pain to be rated from “no pain” to “worst pain imaginable.” The pain diagram documents the patient’s extent of pain and allows the pain to be monitored. Pain diaries reviewed periodically by the physician encourage patient involvement and are useful for outcome assessments. A detailed history of the onset and nature of pain is important. Next, the physician should perform a detailed neurologic and musculoskeletal examination. Electromyography and nerve conduction studies are useful in assessing large-fiber involvement and the presence of axonal loss and reinnervation. Assessments of small-fiber pathology with dermal biopsies or quantitative sensory testing remain principally research tools. Referrals to appropriate specialists for help in pinpointing a diagnosis allow for use of disease-based therapies, when available. Finally, for patients in whom concomitant psychological dysfunction is suspected, psychological screening for depression and anxiety should be performed. The Beck Depression Inventory and other psychological assessment tools can be used for mood assessment.

**Approach to Pharmacotherapy**

Despite improvements with pharmacotherapy, up to 30% of patients may have intractable pain. Previous medical regimens, including dosing, escalation, and reasons for failure, should be reviewed.

Many drugs are initiated at intolerable doses, escalated too rapidly, and discontinued because of improperly addressed manageable adverse effects. Patients should understand the goals of each step and need to know that effects are not immediate. Serum levels are generally unpredictable of response and should be monitored if maximal doses are achieved without toxicity or benefit. Medications are not necessarily lifelong therapy, and tapering should be considered after a period of sustained relief and improved function.

Many patients, especially those with localized symptoms, may respond to initial therapy with topical lidocaine. In diffuse syndromes, pharmacotherapy begins at the lowest available dose of a single drug, followed by gradual titration to efficacy and tolerability. Initial systemic therapy may begin with gabapentin or nortriptyline. Tricyclic antidepressants should be used with caution in patients with a history of cardiac conduction disturbances. The tertiary amines, such as amitriptyline, should be avoided in elderly persons because of their increased risk of falling. To best evaluate efficacy and possible adverse effects, it is advisable to avoid simultaneous adjustments of an existing regimen and the addition of new agents. Incomplete or partial responses to drugs with minimal risk such as topical lidocaine often can be augmented by the addition of a drug with a different mechanism of action (such as gabapentin). Although many patients respond favorably to 2 or 3 drugs with synergistic profiles, careful attention must be given to the use of more than 3 drugs when incremental benefit does not occur. Physician and patient expectations often must be tempered by the clinical experience of incomplete pain relief in most patients. Improving the activities of daily living is an important goal from the outset of therapy but is also important when a ceiling of analgesic efficacy has been reached with a pharmacological regimen.

Tramadol can be considered a treatment option for patients in whom a TCA or gabapentin fails or is only partially effective, especially when nociceptive pain (eg, from osteoarthritis or cancer) coexists. Many of these individuals will require more potent opioids, and individual tolerability varies widely. Rotation to a different opioid may be useful in patients with poor tolerability to an initial agent. Although opioid abuse is uncommon in patients with chronic pain, many physicians use contracts defining the terms of therapy, including the use of periodic serum and urine drug testing. Patients who may benefit from opioid use can be identified with a trial of a short-acting agent such as hydrocodone, oxycodone, or morphine, depending on the severity of the problem. If the trial is effective, long-term therapy with a sustained-release or long-acting preparation is advisable. A dosing schedule at regular intervals is preferable to use of “breakthrough” medications for patients with chronic pain. Use of nonpharmacological options, such as psychological techniques, TENS, and local modalities (heat, ice, massage) should be encouraged instead of “as needed” or “breakthrough” medications when a stable dose of opioid has been achieved.

**Nonpharmacological Management**

Refractory pain leads to depression, anxiety, impaired productivity, declining social functioning, and diminished quality of life. Characterized by the escalating use of health care, affective disorders, and physical deconditioning, the chronic pain syndrome requires a comprehensive treatment strategy incorporating interdisciplinary management. Nonpharmacological management plays an important role in restoring function and reducing disability. Every effort should be made to normalize the patient’s sleep schedule. Reviewing good sleep hygiene, limiting caffeine intake, and encouraging exercise can prevent dependence.
TABLE 2. Steps for Contemporary Neuropathic Pain Evaluation and Management

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
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<tbody>
<tr>
<td><strong>Diagnostic evaluation</strong></td>
<td><strong>Neurological consultation</strong></td>
<td><strong>Disease-specific tests by subspecialist</strong></td>
</tr>
<tr>
<td>Detailed medical history and physical examination</td>
<td>Neurosurgical consultation</td>
<td>Neuroimaging and Pain clinic referral*</td>
</tr>
<tr>
<td>Neuroimaging and electrodiagnostic studies when necessary</td>
<td>Pain clinic referral*</td>
<td>Pain clinic referral*</td>
</tr>
<tr>
<td><strong>Nonpharmacological management</strong></td>
<td><strong>Patient support groups</strong></td>
<td><strong>Vocational rehabilitation</strong></td>
</tr>
<tr>
<td>Patient education</td>
<td>Physical therapy</td>
<td>Pain rehabilitation program</td>
</tr>
<tr>
<td>Functional assessment</td>
<td>Cognitive behavioral therapy</td>
<td></td>
</tr>
<tr>
<td>Psychological assessment</td>
<td>Sleep hygiene optimization</td>
<td></td>
</tr>
<tr>
<td>Sleep assessment†</td>
<td>Exploration of complementary therapies (eg, acupuncture)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacological management</strong></td>
<td><strong>Second-line agents or adjuvant medications§</strong></td>
<td><strong>Determined by pain medicine specialist</strong></td>
</tr>
<tr>
<td>First-line agents‡</td>
<td>Diagnostic somatic or sympathetic nerve blocks</td>
<td></td>
</tr>
<tr>
<td>None; pursue nonpharmacological and pharmacological management first</td>
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*Include early referral to a pain clinic if diagnostic somatic or sympathetic nerve blocks are warranted.
†Patient’s sleep hygiene should be reviewed, and complementary medicine may be considered.
‡When instituting pharmacological agents, primary care physician should administer adequate trials (usually 6-8 weeks) of first-line agents (Table 1). Dose should be escalated until intolerable adverse effects occur or until efficacious.
§Consider if first-line agents have been ineffective. Adjuvant medications include sleeping agents, muscle relaxants, antidepressants, and anxiolytics.

on a nightly sedative. Psychological referral for biofeedback, cognitive-behavioral techniques, group therapy, and counseling is warranted early in patients with psychosocial impairment. Physical therapy referral should be made for neuromuscular rehabilitation, gait and proesthetic device assessment, therapeutic exercise instruction, desensitization (especially in patients with severe allodynia and hyperalgesia), and TENS trials. A structured program with stepwise advancement is imperative in many disorders, especially CRPS and chronic radiculopathy. Occupational therapy and vocational rehabilitation may help the patient transition to functional independence. The network of care completed by mental health providers and physical and occupational therapists often helps sustain patient optimism and participation. These interventions are summarized in Table 2.

**INTERVENTIONAL THERAPY**

Interventional therapy (diagnostic or therapeutic nerve blocks or implantable technologies) may be considered in patients with continuing pain and dysfunction who are unresponsive to conservative approaches. Techniques such as local anesthetic and corticosteroidal nerve blocks generally are used to hasten return of function while long-term strategies are identified. Although evidence for the efficacy of epidural injections is limited, in some cases success rates are higher than with conservative therapy. Patients with acute neck or back pain with a radicular pattern may derive the greatest benefit from epidural corticosteroid injection. The primary care physician may consider interventional strategies such as epidural corticosteroid injections in acute radiculopathy if symptoms persist despite physical therapy and use of oral analgesics.

In CRPS, early physical rehabilitation of the affected limb is crucial for recovery. If the patient is unable to undergo physical therapy despite adequate medication trials, referral to a pain clinic is appropriate. Nerve blocks such as a lumbar sympathetic block (lower extremity), stellate ganglion block (upper extremity), or somatic nerve block may provide sufficient analgesia for participation in physical therapy and remobilization. The duration and extent of analgesia should be considered when determining the need for subsequent nerve blocks and escalation of physical therapy.

After multiple medication trials have been ineffective, referral to a pain clinic is warranted for additional medical management and appropriate interventions by the pain specialist. A trial of SCS may be indicated for certain NP diagnoses. The positive results of SCS for patients in whom other therapies have failed for low back pain syndrome and CRPS have led to the use of SCS in other neuropathic disorders. Also, in a cost-effectiveness analysis of SCS vs conventional medical treatment, SCS was cost-effective after 2.5 years of follow-up and resulted in more patients returning to work than patients in the medical management group. In selected patients, intrathecal pharmacotherapy offers the potential for targeted therapy of the spinal cord. Intrathecal opioids, clonidine, baclofen, and...
local anesthetics (alone or in various combinations) have been used long term in selected patients with refractory pain. For example, intrathecal morphine has been used successfully in patients who respond to oral opioids but have unmanageable adverse effects. Intrathecal drug delivery should be considered early in patients with NP and in whom systemic analgesics are poorly tolerated.

CONCLUSION

Neuropathic pain is widely prevalent and associated with so many diverse diseases that the primary care physician is bound to encounter many cases during his or her career. During the initial evaluation, it is important to ask questions pertaining not only to the patient’s pain state but also to ongoing activities of daily living, mood, and sleep. Medication trials may begin with a recommended first-line agent, but eventually, opioids or polypharmacy may be necessary. Along with medications, physical therapy, a TENS trial, and sleep optimization may improve the patient’s chances for a successful, functional outcome. Despite the wide variety and number of medications available for treatment of NP, patients and clinicians must be prepared for the modest effects achieved with most therapies. In patients with refractory pain, a multidisciplinary approach may be necessary, which may include referring the patient to a pain specialist for advanced pain-management techniques.

REFERENCES


