Neuropathic pain: Etiology, pathophysiology, mechanisms, and evaluations

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Introduction

Reports of more than a century of medical observation and research have demonstrated that neuropathic pain is more definitive than merely a concept or a single disorder: It is instead an evolving collection of established clinical and experimental conditions all of which share the perpetuation of manifested pain symptoms or pain-related behaviors created by neural tissue injury other than that involved with simple nociception.\(^1,2\)

While neuropathic pain has been operationally defined as an abnormal pain state that arises from a damaged peripheral nervous system (PNS) or central nervous system (CNS),\(^3\) there is supporting evidence suggesting that several disease states within this category have active residual involvement of nociceptors at the site of the original injury, creating a mixed nociceptive–neuropathic pattern. Several painful disorders categorized as neuropathic are created or maintained by aberrant neural communication involving autonomic nervous system pathways that are not considered to be purely peripheral or central. These include complex regional pain syndromes types I and II (reflex sympathetic dystrophy and causalgia, respectively) and sympathetically maintained pain (SMP).\(^4,5\)

Neuropathic pain syndromes

In primary care as well as many types of specialty practice, the term neuropathic pain has been most often thought of as simply meaning painful peripheral neuropathy, as commonly occurs in severe diabetes mellitus (DM). This association may have developed based upon the high incidence of diabetes, and the bilateral, distal distribution of other symptoms (sensory loss), and signs (reduced temperature and circulatory compromise) commonly revealed in this illness. In general clinical practice, the pains of well-known neurological disorders, such as those created by herpes zoster and inflammatory involvement of the trigeminal nerves are more likely to be perceived as focal neuralgias, rather than neuropathic pain. Similarly, the pain created by local compression of nerve roots is considered to represent just one aspect of a radiculopathy rather than being part of a neuropathic pain syndrome. Even when contralateral pain is created by unilateral thalamic or other deep hemispheric infarctions, the symptoms are initially thought...
to represent a specific (central poststroke) syndrome, rather than reflecting a portion of a more general (neuropathic) pain category.

In addition to those syndromes mentioned in the preceding paragraph, there are several common, clearly identified conditions that are known associations to severe, persistent neuropathic pain.

**Neuropathic pain disorders by etiology**

In theory, almost any of the pathological processes known to create damage or dysfunction to neural tissue can be considered as potential causes for neuropathic pain. Viral, bacterial, aseptic inflammation, pressure due to neoplasm or other structural lesions, degenerative, ischemia, autoimmune, toxic, traumatic, and endocrine/metabolic mechanisms have all been implicated in the production of pain (Tables 1). A general list of adjuvant analgesics for neuropathic pain can be seen in Table 2 and will be discussed in detail in the second part of this article.

**Pathophysiologic processes subserving neuropathic pain**

Predictably, there is substantial evidence that abnormal nerve activity is an important mechanism underlying the spontaneous pain typical of neuropathic pain states. It is hypothesized that sites of ectopic foci include developing on injured or regenerating nerves in the periphery, at the level of the nociceptor, neuromas, or segments of injured nerves; at the dorsal root ganglion; and in the dorsal horn laminae of the spinal cord. Indeed, after nerve transection, increased sensitivity occurs, followed in a few days by spontaneous activity. These abnormal ectopic foci may be thought of as spontaneous pain generators, resulting in paroxysmal and spontaneous pain.

**Table 1**

<table>
<thead>
<tr>
<th>Common causes of neuropathic pain</th>
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<tbody>
<tr>
<td><strong>Polyneuropathy</strong></td>
</tr>
<tr>
<td>Diabetes (insulin-dependent and non-insulin-dependent)</td>
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<tr>
<td>Alcoholism</td>
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<tr>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Hypothyroidism</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Chemotherapy (vincristine, cisplatinum, paclitaxel, and metronidazole)</td>
</tr>
<tr>
<td>Anti-HIV drugs</td>
</tr>
<tr>
<td>B-12 and folate deficiencies</td>
</tr>
<tr>
<td>Fluoroquinolones (peripheral neuropathy)</td>
</tr>
<tr>
<td><strong>Small-fiber neuropathy</strong></td>
</tr>
<tr>
<td>Mononeuropathy</td>
</tr>
<tr>
<td>Entrapment syndromes</td>
</tr>
<tr>
<td>Traumatic injury</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>Plexopathy</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Avulsion</td>
</tr>
<tr>
<td>Tumor</td>
</tr>
<tr>
<td><strong>Root syndromes and radiculopathy</strong></td>
</tr>
<tr>
<td>Compressive lesions</td>
</tr>
<tr>
<td><strong>Cervical and lumbar radiculopathy</strong></td>
</tr>
<tr>
<td><strong>Neuropathic low back pain</strong></td>
</tr>
<tr>
<td>Inflammatory</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
</tr>
<tr>
<td>Phantom limb pain</td>
</tr>
<tr>
<td>RSD/causalgia/CRPS</td>
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</tbody>
</table>
Precise pathophysiology is unclear, but pharmacological evidence suggests that ectopic activity is due to an increased number of sodium channels, or more likely an abnormal subtype of sodium channel, resulting in unstable sodium channel activity. Pharmacological evidence supporting this hypothesis is the effectiveness of local anesthetics and some anticonvulsants (sodium channel-blocking drugs) in treatment of neuropathic pain. These pharmacotherapies presumably produce frequency and voltage-dependent blockade of sodium channels on damaged neurons. The abnormal sodium channel involved in neuropathic pain states may be a tetrodotoxin-insensitive subtype, found only in the neural tissue. Accumulation of atypical as well as tetrodotoxin-sensitive sodium channels (responsible for normal nerve conduction) may explain the often inadequate therapeutic benefit of current sodium channel-blocking pharmacotherapies.

Table 2

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Mechanism of drug action</th>
</tr>
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<tbody>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Sodium channel blockade; sodium and calcium channel modulation, GABA and glutamate events, chemically related to tricyclic antidepressants</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Prodrg- MHD (10-OH metabolite) blocks voltage gated Na channel, increas K conductance, modulates high voltage activated Calcium channels</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Na/Ca channel blockade, glutamate antagonism, GABA facilitation, carbonic anhydrase inhibition</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Gltamate inhibition, Na channel inhibition, 5-HT3 inhibition</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>MAY inhibit N-Type Na channel, inhibition of GABA, reduction of delayed rectifier K current</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Sodium channel blockade</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Sodium channel blockade</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Calcium channel binding</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Calcium channel binding</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>GABAergic mechanism</td>
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<tr>
<td>Antidepressants</td>
<td></td>
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<tr>
<td>Tertiary amines</td>
<td></td>
</tr>
<tr>
<td>(amitriptyline</td>
<td></td>
</tr>
<tr>
<td>imipramine)</td>
<td>As a group norepinephrine and serotonin reuptake effects, possible NMDA effects, and sodium channel blockade</td>
</tr>
<tr>
<td>Secondary amines</td>
<td></td>
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<tr>
<td>(desipramine,</td>
<td></td>
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<tr>
<td>nortriptyline)</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Monoamine reuptake blockade, of NE, 5-HT, and desensitize adeny cyclase, down regulate beta and 5-HT receptors, non-therapeutic receptors anticholinergic, alpha adrenergic and H1 receptor events</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Monoamine reuptake blockade, of NE, 5-HT, and desensitize adeny cyclase, down regulate beta and 5-HT receptors, non-therapeutic receptors anticholinergic, alpha adrenergic and H1 receptor events</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Monoamine reuptake blockade, of NE, 5-HT, and desensitize adeny cyclase, down regulate beta and 5-HT receptors, non-therapeutic receptors anticholinergic, alpha adrenergic and H1 receptor events</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Monoamine reuptake blockade, of NE, 5-HT, and desensitize adeny cyclase, down regulate beta and 5-HT receptors, non-therapeutic receptors anticholinergic, alpha adrenergic and H1 receptor events</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Serotonin-selective effects</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Serotonin-selective effects</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Adrenergic and opioid receptor-binding effects, 5-HT inhibition</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Serotonin-norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>As a group sodium channel-blocking effects</td>
</tr>
<tr>
<td>Mexiletine</td>
<td></td>
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<tr>
<td>EMLA cream</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>Acts at (\mu) opioid receptors and as a serotonin and norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>Acts on (\mu) opioid receptor and noradrenergic and serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Anti-inflammatory and membrane-stabilizing effects</td>
</tr>
<tr>
<td>Baclofen</td>
<td>GABA-B agonist</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Vanilloid agonist and C-fiber neurotoxin</td>
</tr>
</tbody>
</table>
Research work in animal models demonstrates that voltage-dependent calcium channels may also be important in modulating neuropathic transmission. Unfortunately, the currently available calcium channel blockers are cardio-selective, but some AEDs are calcium channel blockers and are not particularly effective in neuropathic pain. There appear to be at least six calcium channel subtypes, and studies with novel N-type calcium channel blockers are promising in animals. Preliminary studies with conotoxin (SNX-111) are positive, although the drug must be administered intrathecally.

Gabapentin and pregabalin, novel gabapentenoid anticonvulsants, appear to bind to the α2delta subunit of a voltage-dependent calcium channel. Work by Chaplan demonstrates that messenger RNA and protein for the α2d subunit are increased more than 10-fold in the dorsal root ganglia following nerve injury, but are not changed after other forms of tissue injury. Blockade of a retrograde signal from the injury site (which may involve nerve growth factor) prevents up-regulation of the α2d subunit. Chaplan points out that the α2d subunit does not seem to play a role in normal channel kinetics but may affect calcium channel assembly and insertion into the neuronal membrane. Thus, the subunit may act as a drug-binding site and secondarily modify channel kinetics. These agents can have associated cardiac events.

Neuropathic pain disorders

Diabetic neuropathy

The most recent IASP definition of neuropathic pain, as noted earlier, is “pain initiated or caused by a primary lesion or dysfunction in the nervous system.” It is felt that there are three general phases of pain: phase 1—transient activation of the nociceptive system occurs secondary to appropriate stimuli and CNS processing of this stimulus induced information occurs appropriately; phase 2—each injury evokes mechanisms representing nociceptive system plasticity and which induces reversible modulation of the nociceptive system; phase 3—modification of the nociceptive system induces chronic abnormal pain sensations.

These mechanisms may be activated in a different order, which would help to explain the clinical differences between nociceptive and neuropathic pain.

In nociceptive pain, tissue damage occurs, activation of phase 1 is noted, after peripherally occurring pain, which is conducted to the central nervous system (CNS)—pain modulation in phase two occurs, including peripheral and central sensitization—these changes may last hours to days and then modification of pain sensation (in phase 3) can occur, particularly in disorders involving chronic inflammatory processes, causing prolonged changes to responsiveness, leading to chronic pain. In neuropathic pain, damage to the nervous system induces the changes to phase 3 first, secondary to loss of function, inducing modification of pain sensation, which is followed by activation of phase 1 (activation of the nociceptive system) by ectopic activity secondary to changes in the nociceptive system and then modulation in phase 2 occurs, which is effected by central sensitization, disinhibition, and descending facilitation.

Diabetic neuropathy (DN) is a broad term for several different clinical syndromes, with different pathophysiological mechanisms.

Diabetes is probably the most common cause of neuropathy in primary care, and diabetic neuropathy is probably the most common neurological problem associated with diabetes. The incidence of DN increases with the duration of diabetes, the degree and duration of hyperglycemia, and its treatment. Further epidemiologic data indicate that between 30% and 40% of type 2 diabetics have a distal peripheral neuropathy. The Diabetes Control and Complications Trial study found the annual incidence of neuropathy was 2% per year, but with intensive treatment of type 1 diabetics, it dropped to 0.56%. They found that other risk factors included the duration of diabetes, age, cigarette smoking, hypertension, height, and hyperlipidemia.

In general, the prevalence of DN varies from 5% to 100%, secondary to questions regarding the diagnosis.
The definition of diabetic neuropathy, according to the San Antonio Consensus Statement on Diabetic Neuropathy, is a demonstrable disorder, subclinical or clinical, occurring in the presence of diabetes mellitus without other causes for peripheral neuropathy. Furthermore, the diabetic peripheral neuropathy includes somatic and/or autonomic manifestations.

There are a number of mechanisms of peripheral neuropathic pain, including peripheral neuronal sensitization, spontaneous ectopic electrical discharges, collateral sprouting, and ephaptic communication. Centrally, there are also problems including disinhibition, central sensitization and synaptic reorganization, and connectivity in the spinal cord laminae of the dorsal horn.

The pathophysiology of painful diabetic neuropathy (PDN) is also multifactorial, with both somatic and autonomic neuropathies.

Somatic neuropathies include both mononeuropathies and polyneuropathies, while the autonomic neuropathies affect the cardiovascular system, along with the gastrointestinal and genitourinary systems, among others.

Still another classification includes symmetrical neuropathies and focal and multifocal neuropathies.

The most common form of diabetic neuropathy is distal sensory or sensorimotor polyneuropathy, which involves both AB, A delta, and small C-unmyelinated nerve fibers. Small-fiber sensory neuropathies can include a number of characteristics and include hypoxia as well as distal axonopathy with dying back of the nerve as primary pathoetiology. The small-fiber sensory neuropathy includes hyperalgesia, paresthesia, burning pain, lancinating pain, loss of pain and temperature sensation, loss of visceral pain, and eventual foot ulceration, leading to an increased incidence of amputation.

In the presence of a large-fiber sensory neuropathy, one can find loss of vibration and proprioception and areflexia on neurological examination and abnormal nerve conduction studies.

The distal symmetrical sensorimotor polyneuropathy begins insidiously and can involve both large and small fibers. The distal lower extremities are the first anatomic sites to be affected. The sensory symptoms typically advance up above the knees and include the distal upper extremities and the anterior aspect of the trunk; the vertex of the head may also rarely be involved.

Symptoms may be positive (burning pain, paresthesia, lancinating pain, hyperesthesia, and allodynia) and/or negative (numbness).

There are also a number of symmetrical neuropathies associated with diabetes. Hyperglycemic neuropathy is associated with paresthesias in the extremities and the trunk and is most frequently seen in poorly controlled diabetic patients, or those who are newly diagnosed, and will improve with a higher level compliant glycemic control.

Acute painful neuropathy (diabetic neuropathic cachexia) is usually seen in older men with a history of significant weight loss associated with the sudden appearance of severe burning pain in the extremities, occasionally the trunk, autonomic dysfunction, sensory loss, and less commonly muscle weakness.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is associated with diabetes. Patient presentation includes symmetric weakness associated with demyelination (on nerve biopsy) and changes on electromyography. Pain distribution is less likely to be symmetric. Patients with CIDP associated with diabetes mellitus differs from idiopathic CIDP in that the diabetic patients are typically older; have a longer duration of symptoms, significant axonal loss, and less commonly muscle weakness.

Asymmetric, focal, and multifocal neuropathies are also found in diabetic patients. Diabetic amyotrophy (also known as asymmetrical proximal lower-limb neuropathy, diabetic polyradiculopathy, and diabetic lumbosacral radiculoplexus neuropathy) is most frequently seen in type 2 diabetics in their fifth or sixth decades. It is associated with unilateral symptoms initially, becoming bilateral. An asymmetrical proximal motor neuropathy is seen in association with pain in the back, hip, and knees. Muscle wasting and weakness are seen in the hip flexors, adductors, and quadriceps. There is a loss of the quadriceps reflex. The patellar reflex is also decreased ipsilaterally. Pain is acute or subacute. The disorder appears to be immunological in nature.

Diabetic cranial neuropathies most typically affect the oculomotor nerves (third, fourth, and sixth), facial nerve (seventh), and fifth cranial nerves. The optic nerve can also be affected.
Clinically, patients may develop mild or severe periorbital pain and/or headache followed by diplopia. It is associated with muscle paresis with sparing of the pupillary reflex, decreased blink reflex, and, rarely, nonarteritic acute anterior ischemic optic neuropathy (NAION) without the presence of pre-existing diabetic retinopathy.30–33

Truncal mononeuropathy (also known as thoracoabdominal neuropathy, thoracolumbar radiculopathy, and thoracic radiculopathy) is most frequently seen in middle-aged patients, typically those with essentially mild diabetes. Both positive and negative sensory signs may be evident, including pain in the back, abdomen, or chest in the distribution of thoracic and/or upper lumbar nerve roots, and associated areas of sensory loss or dysesthesia in dermatomal distributions. The pain can be severe burning, stabbing, belt-like, deep, and aching, and is more intense at night. The pain begins unilaterally and then becomes bilateral. In some patients, hyperalgesia and allodynia may occur. Weakness of the abdominal wall can be seen, associated with abdominal muscle paresis. Diabetic distal symmetric polyneuropathy is frequently also present.26,34,35

Mononeuritis multiplex is an asymmetrical sensory and motor peripheral neuropathy associated with damage to at least two nerves. It can later become symmetric. The disorder, which is associated with systemic disorders such as diabetes, rheumatoid arthritis, and vasculitis, can get worse over time. The associated nerve damage appears to be secondary to axon destruction.36

Diabetic autonomic neuropathy is frequently overlooked. It can affect any organ of the body that is innervated by autonomic nerves. Parasympathetic dysfunction has been found in 65% of type 2 diabetics at 10 years postdiagnosis of diabetes; combined sympathetic and parasympathetic neuropathy is found in 15.2% of patients.22 There are numerous symptoms found in autonomic neuropathy in various systems: cardiovascular—postural hypotension, resting tachycardia, painless myocardial infarction, prolonged QT interval, and sudden death; gastrointestinal—esophageal motor incoordination, gastric hypomotility, pylorospasm, uncoordinated intestinal motility or diabetic diarrhea, constipation, fecal incontinence, and gall bladder hypomotility; genitourinary—impaired bladder sensation, atonic bladder, post-micturation dribbling, detrusor hyporeflexia or hyperreflexia, male impotence, problems with ejaculation, dyspareunia, and reduced vaginal lubrication in women; thermoregulatory—sudomotor and vasomotor changes; pupillary—miosis, disturbances with dilatation, and the Argyll Robertson pupil. There is a question as to the presence of impaired ventilation and sleep apnea. Gustatory sweating is the most common symptom followed by postural hypotension, diarrhea, sexual dysfunction, anhidrosis of the feet, bladder abnormalities, and gastroparesis.24,37–41

Clinical evaluation of the cardiovascular signs of diabetic autonomic neuropathy, particularly in patients with a 5-year history of diabetes or longer, should be performed and include at least postural blood pressure changes as well as heart rate variability with respiration.42

Type 1 diabetic patients with cardiac autonomic neuropathy can have a greater risk of sudden death possibly associated with prolongations of the QTc interval.43–49 Type 1 diabetic patients with autonomic neuropathy have decreased myocardial perfusion capacity when given a vasodilator, which may be part of the cause for increased mortality in these patients, possibly secondary to defective myocardial sympathetic vasodilatation, the lack of the ability to maintain blood pressure during vasodilatation, or both.50 It has even been suggested that cardiac autonomic neuropathy may contribute to a “dead-in-bed syndrome” associated with decreased vagal tone and predominant sympathetic tonus increasing the possibility of cardiac arrhythmia during significant bouts of hypoglycemia.51,52 This would also be associated with a higher risk of arrhythmia and sudden death after acute myocardial infarction and with co-administration of multiple or single QTc prolonging pharmacotherapies.53,54

As the risk of cardiovascular events in patients with diabetes is estimated to be 2–4 times higher than in normal individuals, a thorough clinical evaluation should be routinely done.55,56 It should also be noted that the diabetic cardiac autonomic neuropathy develops independently from the painful, somatic diabetic neuropathy.57

Compression neuropathies (entrapment neuropathies) are uncommon. The median nerve is most commonly affected. The ulnar or lateral femoral cutaneous nerve may also be affected.24,58
Mechanisms of diabetic peripheral neuropathy

The theoretical constructs include metabolic, vascular, altered neurotrophic support, autoimmune, and free radicals associated with oxidative stress.

Hyperglycemia and the polyol pathway

Hyperglycemia is the primary reason for the development of diabetic neuropathy as has been demonstrated by the Diabetes Control and Complications Trial (DCCT). This group also showed that with excellent control of hyperglycemia there is a significant reduction of autonomic dysfunction (53%), neuropathy (64%), and motor conduction velocity changes (44%) in type 1 diabetics.

Insulin is not responsible for glucose uptake in the peripheral nerves. For this reason, high glucose levels in the blood cause high nerve glucose concentrations. The polyol pathway, via reactions catalyzed by aldose reductase, converts glucose to sorbitol. Nerve fructose levels are also increased. Excess fructose and sorbitol induce a decrement in the expression of the sodium/myoinositol cotransporter, which causes decreased myoinositol levels. This, in turn, creates decreased levels of Na/K ATPase activity. Aldose reductase, when activated, depletes its cofactor nicotinamide–adenine dinucleotide phosphate (NADPH), which causes decreased levels of nitric oxide and glutathione, which work to stop oxidative injury. The lack of nitric oxide stops vascular relaxation, which helps in the induction of chronic ischemia.

Microvascular ischemic changes in the nerves of diabetes can include endothelial cell hyperplasia, thickening of the capillary basement membrane, and neuronal ischemia and infarction. Endoneurial vascular resistance to hyperglycemic blood may induce endoneurial ischemia.

Neurotrophic factors are needed for the maintenance of nerve function and structural maintenance. Nerve growth factor (NGF) has been found to be decreased, and, along with insulin-like growth factor-1, shown to correlate with the severity of diabetic neuropathy in animals. Insulin has neurotrophic effects and in a diabetic state, its deficiency may be associated with the development of neuropathy.

Autoimmune neuropathy is felt to emerge from immunogenic changes of the cells in the endothelial capillaries.

Dysfunction of the sodium channels have been found in animal models of painful neuropathy. Increased activity of voltage-gated calcium channels has also been demonstrated in diabetic neuropathy, which can lead to tissue injury.

Oxygen free radicals may induce nerve damage directly or by inhibiting nitric oxide production, and thus causing a reduced nerve blood flow. Free-radical generation is increased in diabetics by the processes of non-enzymatic glycation and polyol pathway. At the same time, the ability to neutralize free radicals is decreased because nicotinamide–adenine dinucleotide phosphate (NADPH), which deals with cell oxidation/reduction status, is diminished as it is consumed by increased activity of aldose reductase.

Activation of protein kinase C (PKC) occurs secondary to hyperglycemia, which leads to increased diacylglycerol synthesis and PKC activation. PKC may also be activated by oxidative stress. It increases vascular permeability, blood flow changes, and impairment of nitric oxide synthesis.

Another possible mechanism is derangement of the essential fatty acid pathways from linolenic acid to prostaglandins and thromboxane, which can induce cellular dysfunction in a number of areas, including membrane fluid abnormalities, a decrease in prostaglandin E2, and changes in the membrane of red blood cells.

Finally, circulating nerve growth factor is decreased in diabetic patients with neuropathy. Treatment with nerve growth factor has shown improvements in peripheral nerve growth and function.

Regardless of the pathophysiological mechanism, or combination of mechanisms that coalesce to induce the production of diabetic neuropathy, chronic poorly controlled hyperglycemia appears to have a significant if not pivotal role in its pathoetiology.
Small-fiber neuropathy

Small-fiber neuropathy (SFN) is a common peripheral nerve disease, typically idiopathic in etiology, which commonly presents in middle-aged and older people with burning pain in their feet and/or symptoms of autonomic dysfunction.\textsuperscript{77–79} The disorder selectively involves small-diameter myelinated and unmyelinated nerve fibers. Frequently, autoimmune disorders/mechanisms are suspected but rarely found. SFN can be caused by disorders of metabolism (diabetes), chronic infections (such as human immunodeficiency virus), genetic abnormalities, amyloidosis, drug toxicity, inherited sensory, and autonomic neuropathies. It may be focal or multifocal.\textsuperscript{15,16}

Diagnosis is most commonly made on the basis of the clinical picture, normal nerve conduction studies (standard electrophysiological tests for nerve injury do not detect small-fiber function), and abnormal specialized tests of small nerve fibers, including biopsy assessment of epidermal nerve fiber density, temperature sensation tests for sensory fibers (quantitative sensory testing for heat and cold), sudomotor testing, and cardiovagal testing for autonomic fibers.\textsuperscript{78,79}

The associated pain is typically secondary to injury to small, unmyelinated C-fiber nerve axons. The pathogenesis of neuropathic pain commonly involves the loss of peripheral axons and inappropriate peripheral and central adaptation of neuronal signaling secondary to this loss.\textsuperscript{80}

Clinically, patients with SFN may present with either positive sensory symptoms (burning, tingling, prickling, lancinating, or aching pain) or negative symptoms (numbness, tightness, and coldness). They may develop allodynia. A feeling of cramping is not uncommon. The symptoms are usually distal. They can be patchy or diffuse. The symptoms are typically exacerbated at night.\textsuperscript{78}

Of interest is that even subclinical small-fiber neuropathy may present with late-onset restless-legs syndrome.\textsuperscript{81} While restless-legs syndrome (RLS) is primarily classified as a sleep disorder, it may be associated with subclinical small-fiber neuropathy, as well as, possibly, dysfunction of the postsynaptic dopamine receptors related to iron metabolism of the CNS, as well as opiate receptors.\textsuperscript{82} Another study noted RLS frequently associated with acquired neuropathies, especially dysimmune neuropathies, particularly small-fiber sensory neuropathies.\textsuperscript{83}

Pain can also occur with large-nerve fiber dysfunction.

Autonomic symptoms may include increases or decreases in diaphoresis, facial flushing, skin discoloration, dry eyes, and xerostomia, as well as possible changes in skin temperature and erectile dysfunction (up to 40% of males)\textsuperscript{78,84,85}

On examination, clinical findings may include a decrease in temperature and pain sensitivity in a patient with normal strength, proprioception, and normal tendon reflexes. Vibration sensation is commonly normal, but some loss in the great toes can be consistent with mild large-fiber involvement. In many patients, especially those who cannot receive specialized testing, their clinical examination may be entirely normal or only minimal/mild findings are noted.\textsuperscript{86,87}

Testing for SFN may include nerve conduction studies, which assess large-fiber function, so they would be normal in the presence of only SFN. They are often within normal limits. It should be noted that patients with SFN may also have some large-fiber loss/dysfunction.\textsuperscript{88}

Special testing for SFN includes the following:

1. \textit{Sympathetic skin response}: This reflex change, which looks at small-fiber sudomotor function in the sweat-related skin electrical potentials, can be measured on electromyographic equipment (EMG). The sensitivity of this test for SMN is thought to be low.\textsuperscript{78}
2. \textit{Quantitative sensory testing (QST)} used for diagnosis of SFN. Temperature testing (hot and cold) is performed. This technique may be used for serial measurements.\textsuperscript{89–91}
3. \textit{Quantitative sudomotor axon reflex test (QSART)} looks at postganglionic sympathetic sudomotor function. This test has a relatively high level of sensitivity in detecting SFN.\textsuperscript{85,90,92}

Other sudomotor function tests include the thermoregulatory sweat test, the Silastic skin imprint method, and the EpiScan, a fast, painless, sensitive selective tissue conductance method for evaluating sudomotor dysfunction in SFN.\textsuperscript{90} Sudomotor testing was also found to be an excellent tool in the evaluation/detection of SFN in another study by Low et al.\textsuperscript{93}
The pathological aspects of SFN have also been closely evaluated. An antibody against protein gene product 9.5, which is present in all axons, was developed in the early 1980s. This enabled immunohistochemical use to help determine, in skin punch biopsies, small-fiber density, which can be found to change as a SFN develops. The reduction of intraepidermal nerve density is the most commonly reported abnormality in skin biopsy, with morphological changes found in the epidermal nerves and underlying subepidermal nerve plexus. Another group indicated that intraepidermal nerve fiber density may be a useful endpoint measure for future neuropathy treatment trials—the main problem being the paucity of laboratories actually doing this work.

The most common cause of a SFN is typically not found, but when it is, diabetes mellitus is frequently the etiology. Idiopathic small-fiber neuropathy is the largest diagnostic category. A subset of diabetic polyneuropathy patients appears to have symptomatic, primarily small-fiber involvement, with or without autonomic dysfunction.

Another group looked at the nerve axon reflex-related vasodilation (N–V response) as a method to evaluate C-nociceptive fiber function. They thought that the N–V response is a reliable tool to diagnose small-fiber dysfunction, which was found early in the natural history of diabetic neuropathy. Sorensen et al. found quantitative small nerve sensory testing a useful tool to detect the presence of neuropathy. They note that small nerve fiber abnormalities do not predict the presence of pain in diabetic neuropathy, and that more severe loss of intraepidermal nerve fibers can be associated with the presence of neuropathic pain in those patients with little or no sign of neuropathy.

Other research has found that impaired glucose tolerance (prediabetes) is associated with an “idiopathic” SFN.

Some other diagnoses related to SFN include the following:

- Chronic alcohol-dependent subjects, possibly via the direct toxic effect of alcohol on peripheral nerve fibers; painful alcoholic polyneuropathy affects the small myelinated and unmyelinated fibers more than large fibers, particularly early in the disease process. Hyperglycemia and impaired vitamin B(12) utilization may also be involved.
- Symptomatic HIV neuropathy, as a measure of small sensory fibers (decreased intraepidermal fiber density and abnormal cold and heat pain thresholds) appears to be associated with transition to symptomatic HIV-associated distal sensory neuropathy up to 6–12 months later.
- Celiac disease, a T-cell mediated autoimmune disorder resulting from a lack of tolerance to gluten, is also associated with SFN as seen on skin biopsies. Idiopathic ataxia may also be present.
- Sjogren syndrome patients with neuropathy exhibited either a decreased intraepidermal nerve fiber density or abnormal nerve morphology.
- Systemic lupus erythematosus (SLE), an inflammatory, autoimmune disease, is also found to be associated with a pure small-diameter nerve fiber neuropathy.
- Vasculitic neuropathy has infrequently been associated with skin denervation in spite of many manifestations of SFN, including reduced sensitivity to QST and neuropathic pain; epidermal nerve fiber densities were decreased, in addition to the more typical vasculitic effect on large diameter nerves.
- A case report of four patients with SFN responsive to steroid usage indicates that the patients had acute-onset neuropathic pain, normal EMGs, and provocative/diagnostic QST and skin biopsies. The authors raised the question of this being a new entity.

Other hereditary disorders may be associated with SFN, including hereditary sensory autonomic neuropathies I and II, burning feet syndrome, amyloidosis, Fabry’s disease, and Tangier disease.

Treatment of SFN is not really different from that of large-fiber neuropathies. If an identifiable cause is found, it should be treated. Most commonly, the goal of management of SFN is amelioration of pain, using the same drug classes used for more common neuropathic pain syndromes: anticonvulsants (AEDs), tricyclic antidepressants (TCAs), SNRIs, opioids, and topical agents.
HIV-associated neuropathic pain

Distal symmetrical polyneuropathy (DSP) associated with HIV infection is the most frequent neurological complication of the disease.\textsuperscript{111} Spontaneous or evoked pain is the most common symptom of DSP.\textsuperscript{112} Aside from DSP, patients may develop mononeuritis multiplex and progressive polyradiculopathy.

The actual pathophysiology of HIV neuropathy is not known. DSP, as noted above, is associated with injury or loss of primary afferent fibers inducing distal axonal degeneration, “dying back” of the neurons.\textsuperscript{113} This may be mediated by the HIV or by cytotoxic immune processes.\textsuperscript{112}

A direct mechanism is proposed in which the HIV viral envelope glycoprotein gp120 directly invades the peripheral nerve and the dorsal root ganglion, which induces neurotoxicity.\textsuperscript{114,115} The activity of chemokines and gp120 glycoprotein can act on the chemokines receptors of nociceptive neurons and induce both hyperesthesia and allodynia.\textsuperscript{116}

HIV may induce indirect damage by promoting macrophage infiltration in peripheral nerves and the dorsal root ganglia.\textsuperscript{117,118} The macrophages, once in the peripheral nerve, can cause local release of proinflammatory neurotoxic cytokines, such as tumor necrosis factor, interleukin-1, and interleukin-6, which can induce axonal degeneration.\textsuperscript{119–121}

Antiretroviral chemotherapy can also induce a toxic neuropathy.\textsuperscript{122}

Neuropathic low back pain

Low back pain (LBP) is one of the most common disorders, effecting about two-third of the adult population in the USA at some time in their lives. It may or may not be associated with radiculopathy or radiation to the sciatic and/or femoral nerves.\textsuperscript{123} The etiology of the pain may be secondary to a large number of possible problems, making the differential diagnosis large; however, it may be broken down to mechanical, compression, inflammatory, and neuropathic factors, which may be directly affected by social and psychological factors.\textsuperscript{123}

While the degeneration of the intervertebral disc is frequently considered to be the etiology of pain in patients with LBP, it may be more complicated. Degeneration/deterioration of a disc can influence the central nervous system (CNS) by nociceptor stimulation in the annulus fibrosus, which can induce nociceptive pain that is considered to be discogenic pain. This stimulation may be secondary to mechanical or inflammatory factors. While pain with weight-bearing and specific movements is mechanical in nature, there is further growth of both nerve fibers and blood vessels into the deeper layers of the annulus fibrosus.\textsuperscript{124} Algetic substances, including tumor necrosis factor and the interleukins (IL-1β, −6, and −8), may also play a role in the development of LBP.\textsuperscript{124}

In the normal intervertebral discs, only the outer aspects of the annulus fibrosus receive sensory innervation. When discs degenerate, extensive nerve fiber growth is found in the middle third as well as the inner third of the diseased annulus.\textsuperscript{125,126} Some of this nerve growth is associated with the presence of substance P immunoreactivity.\textsuperscript{127} Algetic, inflammatory neuropeptides in the degenerated disc along with possible abnormal mechanical pressure in and upon a diseased, incompetent annulus can induce chemical and mechanical sensitization and stimulation of the nociceptive nerve fibers.\textsuperscript{125}

After the onset of discogenic abnormalities that can initiate pain, after the nociceptors in the disc have been stimulated, the somatosensory system can increase its sensitivity secondary to constant stimulation, causing a nonfunctional response: peripheral sensitization can occur. If the disc degeneration progresses to disc herniation, the nerve roots or dorsal root ganglion, adjacent nervous system structures, may be affected, leading to neuropathic pain of either mechanical or biochemical origin.\textsuperscript{124}

Disc degeneration can also influence other spinal structures including the facet joints, ligaments, and muscles, which individually or as a group can develop into pain generators. This can lead to disc degeneration leading to the development of chronic LBP without being the
actual focus of the pain, with both nociceptive and neuropathic pain being modulated at higher centers (spinal and supraspinally) to develop central sensitization. The central sensitization can be associated with neural plasticity, which can play a significant role in the development and chronicity of pain.

It is also thought that in chronic sciatica, both nociceptive and neuropathic pain components can be distinguished. Neuropathic pain may be secondary to lesions of nociceptive sprouts in the degenerated disc (local neuropathic), mechanical compression of the nerve root (mechanical neuropathic root pain) or secondary to inflammatory mediators (inducing inflammatory neuropathic root pain), all originating from the degenerative disc even without the presence of mechanical compression. There can be several different pain mechanisms inducing sciatic pain, and therefore, it can be designated simply as a “mixed-pain syndrome.”

Kaki et al. looked at the prevalence of neuropathic pain among a sample of 1169 LBP patients using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale. They found that 54.7% of patients had LANSS pain scale scores suggesting a neuropathic type of pain and 45.3% having neuropathic types of pain. Advanced age, female gender, increased height, white race, hypertension, diabetes, a history of smoking, previous back surgery, and previous medications were factors found to be associated with neuropathic LBP.

Bennett et al. note that in the past, pain was divided into two essentially mutually exclusive pain mechanisms: nociceptive and neuropathic. A new approach was looked at, essentially a model of chronic pain which was “more or less neuropathic.” They looked at 200 patients (100 each of nociceptive and neuropathic) and used the LANSS pain scale and the Neuropathic Pain Scale (NPS). They felt that their data supported the theoretical construct that pain can be either functional pain that was non-neuropathic or non-nociceptive, or predominantly neuropathic in origin.

Clinical examination in brief

On history, the patient may report both positive and negative sensory symptoms, including tingling, lancinating, burning pain (positive), or numbness (negative).

The clinician must look at the entire range of peripheral nerve sensation for possible dysfunction, including light touch, pinprick, temperature, and vibration. The use of sudomotor testing for possible associated sympathetic nervous system abnormalities may be useful (see below for more detail).

Treatment in brief

For the chronic LBP patient, a whole-person, bio-behavioral approach is optimal. Pharmacotherapies are important. This article goes into detail regarding the useful anticonvulsant and antidepressant medications for the treatment of neuropathic pain.

Several studies showed that the anticonvulsants topiramate might reduce chronic sciatic in some patients, and bupropion SR was not significantly better than placebo in the treatment of non-neuropathic chronic LBP. The authors of the latter study felt that ADMs that had both noradrenergic and serotonergic effects appeared to have greater efficacy in patients with chronic LBP.

Topical agents may also be useful in the chronic LBP patient, including lidocaine 5% ointment or patch, and capsaicin 0.075%. The use of topical ketamine and gabapentin and/or doxepin may also be given a trial if necessary (see below for more detail).

Central poststroke pain (CPSP)

Central poststroke pain (CPSP) was originally thought to be “thalamic” pain, as described by Dejerine and Roussy, although it was described even earlier in 1883. Dejerine and
Roussy characterized their eponymous thalamic pain syndrome as including hemiplegia; hemiataxia, and hemiastereognosis; difficulties with both superficial and deep sensation; persistent, paroxysmal, typically intolerable pain; and choreoathetoid movements. The reported incidence of CPSP varies widely from 2% to 8% in stroke patients and to 25% in patients with lateral medullary infarctions (Wallenberg’s syndrome).

The onset of the pain may be immediate or be delayed for months to years. The pain may encompass a large part of the contralateral body, but it may also involve only a small area. The pain attributes include dysesthesias, spontaneous or evoked, and burning. Sensory abnormalities are also associated with CPSP. These may include altered sensory processing—warm and cold stimulation applied to the skin may be perceived as paresthesias or dysesthesias rather than cold or warm. Allodynia is encountered in 55–70% of patients. Hyperalgesia and dysesthesia are also frequently observed. Location of the lesions inducing the CPSP is definitively referable to the spinothalamo-cortical tract/pathway, typically associated with abnormal evoked sensations in the peripherally affected area. While at least three thalamic regions that directly or indirectly receive spinothalamic projections appear to be involved in the development of CPSP—the ventroposterior thalamus including the posteriorly and inferiorly located nuclei bordering on that region, the reticular nucleus, and the medial intralaminar region—it is the ventroposterior thalamic region that is proposed to be most significantly involved in central pain. It should also be noted that cerebrovascular lesions located above the diencephalon, i.e., in the parietal lobe, may also induce CPSP.

Sympathetic dysfunction has also been proposed to play a role in central pain secondary to signs of abnormal sympathetic activity: edema, hypohydrosis, trophic skin changes, changes in skin color, and decreased skin temperature. It is also noted that some or many of these changes may be secondary to “movement allodynia,” which makes the patient keep the affected limb motionless.

Reports of CPSP associated with abnormal “epileptiform” activities in thalamic cells may be involved with central pain. This would also indicate some aspects of the problem may be secondary to cortical involvement, as epileptiform discharges typically are associated with that region. Treatment of the CPSP is challenging and may include antidepressants, anticonvulsants, antiarhythmic, antalgics, and non-medication treatment, including transcutaneous electrical nerve stimulation (TENS), dorsal column stimulation (DCS), and deep brain stimulation.

One undesirable effect of repetitive deep brain stimulation (DBS) is the reduction of the seizure threshold, known as kindling. One of the authors is aware of a patient whose pain was only partially reduced with the original stimulus parameters of deep brain stimulation. In an attempt to improve pain control, the individual used the external controller to increase the amount of stimulation above the amount administered by the attending neurosurgeon. After several days of this maneuver, the patient suffered a first-ever focal onset, secondarily generalized seizure. To the authors’ knowledge, this patient may represent the first case of self-induced kindling of seizures in a human patient using DBS for pain control. Other treatments include sympathetic blockade, as well as surgical interventions, including cordotomy, dorsal root entry zone (DREZ) lesions, thalamotomy, or cortical and subcortical ablation.

Complex regional pain syndromes as neuropathic pain

Following peripheral nerve injury, concomitant alternations may be evident in dorsal root ganglia, including transmitter changes and increased density of sympathetic nerve terminals. Tyrosine hydroxylase positive cell terminals that produce norepinephrine migrate from vessels supplying the dorsal root ganglion to nerve ganglion cells following sciatic nerve injury. The dorsal root ganglia then express α-adrenergic receptors. This may be a putative link between peripheral tissue injury, nerve injury, and sympathetically maintained pain states, such as reflex sympathetic dystrophy (RSD) and causalgia (complex regional pain syndromes types 1 and 2, respectively). In the periphery, sprouting nerve terminals may exhibit sensitivity to prostaglandins, cytokines, and
catecholamines. These kinds of changes further increase the complexity of the neuropathic pain picture and blur the distinctions between nociceptive and neuropathic pain.

It should be noted that not all stimulus-independent pain is mediated by spontaneous activity in primary sensory neurons. Loss of normal inhibitory mechanisms, whether segmental, supraspinal, or both, may also cause neuropathic pain. After deafferentation injury, particularly following loss of C fibers, arborization of AB fibers into the substantia gelatinosa of the dorsal horn may result in central sensitization and allodynia. Available evidence supports the contention that tactile allodynia is mediated by large myelinated AB afferents with input that is modulated at supraspinal sites in the dorsal columns.

This may explain why transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation, which produce a low threshold, tingling sensation, characteristic of large-fiber afferent activation, may be effective in chronic pain states, particularly neuropathic pain. Tactile allodynia should be differentiated from thermal allodynia, which appears to be mediated by nonmyelinated C fibers and amplified by pathological spinal dynorphin.

**Postherpetic neuralgia (PHN)**

PHN is a model of neuropathic pain. Its mechanisms differ from those of diabetic neuropathy as well as other models of distal symmetric neuropathy.

This disorder is secondary to a latent infection and reactivation after infection with varicella zoster virus (VZV), which typically inhabits sensory ganglion neurons. Pain is a common clinical concomitant of VZV reactivation.

The prevalence is currently debatable. It is noted that approximately 10% of patients with VZV/ herpes zoster infection will develop postherpetic neuralgia (PHN). The incidence rises with age, with more than 50% of cases in patients older than 60 years. Overall, 50% of these patients are reported to have pain that is refractory to treatment. Another study shows that the pain can precede the eruption of the vesicular rash. It notes that 10–15% of patients with herpes zoster develop chronic postherpetic neuralgia (pain lasting 3 months or more after the rash resolves). While the incidence of PHN does increase with age, a longitudinal study of patients with PHN found that only 48% were symptomatic after 1 year. Another author notes the incidence of PHN to be 400/100,000 per year, with the incidence rising to 12/1000 people over 80 years of age. Finally, the lifetime risk of the development of PHN may approach 20% of the population.

The natural variations of resolution of PHN makes the disorder very difficult to evaluate in a clinical trial, as the natural history of resolution of the diathesis may confound the ability to generalize treatment results of controlled trials in PHN.

PHN is most commonly found in the thoracic dermatomes, followed by the periorbital ophthalmic division of the trigeminal nerve.

The pathophysiology of PHN is noted to be in reality a spectrum with three subtypes: a group with “irritable nociceptors,” who experience minimal deafferentation and touch-evoked allodynia secondary to peripheral nociceptor input, pain that is intensified by capsaicin and relieved by injection of local anesthetics; a deafferentation group with significant sensory loss and no allodynia—anesthesia dolorosa—with possible deafferentation-induced hyperactivity of the CNS nociceptive neurons and/or disinhibition of CNS neurons secondary to loss of pain inhibitory A-β primary afferents or a disruption in descending inhibition; or patients with deafferentation with profound thermal sensory deficit and allodynia, wherein large diameter afferents produce allodynia via new, direct connections to the CNS nociceptors beginning in the dorsal horn of the spinal cord, with central neuronal reorganization. Because of the central changes here, it is felt that these patients will respond better to drugs working against central sensitization rather than drugs with peripheral mechanisms of action.

As treatment is different for this disorder, and should be done in a mechanistic fashion, we will briefly look at it here. In the acute stages, an antiviral agent should be initiated within 72 h, as it can help prevent PHN. The concurrent use of the TCA, amitriptyline, may also be helpful.
The treatment of PHN should include tricyclic antidepressants (TCAs, such as amitriptyline, nortriptyline, and desipramine); serotonin–norepinephrine reuptake inhibitors (SNRIs), such as duloxetine; the AEDs, gabapentin and pregabalin (drugs working on the \(\alpha_{2d}\) subunit of the calcium ion channels); and select opioids and topical lidocaine may also be useful.\(^{188-198}\)

Capsaicin cream has low benefit while the 8% capsaicin patch has now been approved for the treatment of PHN, while epidural steroid and epidural morphine injections have no benefit.\(^{199-203}\) The effectiveness of carbamazepine is unproven,\(^{177}\) as is the use of ketamine,\(^{186,204}\) using non-clinical, evidence-based medicine principles.

**Glial activation in neuropathic pain**

In almost a counterpoint to the above-noted mechanisms of neuropathic pain, it has been reported that astrocytes and microglia in the CNS/spinal cord can be activated and induce the creation and maintenance of pain facilitation secondary to inflammation and damage to peripheral nerves, other peripheral tissues, spinal nerves, and the spinal cord. Glial cells appear to be of immune cell origin.\(^{205,206}\)

Glial activation can occur via a number of processes: bacteria and viruses that bind to specific receptors expressed by both microglia and astrocytes; substance P, excitatory amino acids (EAAs), fractalkine (a unique chemokine expressed by neurons; its only receptor is expressed by microglia),\(^{207}\) and ATP released by A-\(\delta\) and/or C fibers pre-synaptically or by the brain to the spinal cord pain enhancement pathways; as well as nitric oxide, prostaglandins and fractalkine released from “pain transmission neurons.”\(^{208-211}\) After the microglia and astrocytes are activated, they induce hyperexcitability from nociceptive neurons and increased release of substance P and excitatory amino acids from the presynaptic terminals.\(^{208,209}\) These changes are helped by glial release of nitric oxide, EAAs, prostaglandins, proinflammatory cytokines, such as interleukin-1 and -6, tumor necrosis factor, and nerve growth factor.\(^{208,209}\)

These changes create the presence of continuous “pathological pain.”\(^{212}\)

Research indicates that intrathecal gene therapy driving the production of interleukin-10, an anti-inflammatory cytokine, can stop neuropathic/pathological pain.\(^{213}\)

Finally, data suggests that in response to morphine, glia release neuroexcitatory substances, causing opposition to morphine’s analgesic effects.\(^{214}\)

**Diagnostic evaluation of neuropathic pain**

There exist two lines of thought relative to the clinical diagnosis of pain syndromes of this type: one suggests that, since the symptom characteristics of neuropathic pain are not pathognomonic for the condition, their lack of specificity makes the diagnosis difficult to reach.\(^{215}\) Another provides evidence to support certain symptom characteristics as strong indicators of neuropathic pain.\(^{218}\) Regardless of which attitude is correct, the clinician hoping to differentiate neuropathic from non-neuropathic disorders must begin, as always, with the comprehensive clinical history.

It is essential to create a patient-specific, patient-focused, patient-centered, personalized care plan.

**Medical pain history**

The style of medical history that has been modified for the specific documentation of pain has been described in detail elsewhere.\(^{8,217}\)

Within that system the clinician acquires patient-specific information regarding at least eight aspects of the pain problem. A mnemonic often used to ensure that completeness of data collection regarding each characteristic is PQRST, in which P = provocative, palliative factors;
Q = quality; R = region (of onset), radiation, and referred pain; S = severity; and T = timing. Of these characteristics, those that are most commonly considered in the diagnosis of neuropathic pain are quality (burning, shooting, tingling, sharp, or shock-like), timing (continuous or intermittent/paroxysmal), and provocative (stimulus-evoked or stimulus independent). While verbal reports of the regional (spatial) distribution may be helpful in determining the relationship of pain to specific neurological syndromes, the use of a standardized pain drawing instrument (PDI) is preferred for documentation. One tragic error made by clinicians in the past is the dismissal of pain as being organic simply because it did not resemble an anatomic or dermatomal distribution. In fact, types of neuropathic pain that are maintained or mediated through autonomic pathways may follow a pattern of sympathetic sclerotomes or blocks of pain referred from deep muscular or visceral afferent reflexes. In recording pain severity or intensity, it is important to document the patient’s subjective report using standardized scales such as a verbal Numeric Rating Scale (NRS-11) or nonverbal Visual Analog Scale. Even more important is to avoid the cardinal sin of confusing results of a verbal and visual scale by reporting: “the patient stated that his/her Visual Analog Score was 6 out of 10.” For patients with multifocal neuropathic pain or mixed neuropathic/myofascial pain a verbal scale is preferred, since it can be used easily to record intensity for each region, not just the peak or average pain. Finally, it has been suggested that this mnemonic should be changed to add the letter O, for other (associated) symptoms, such as loss of sensation or nonpainful paresthesias or dysesthesia occurring in the same general area as the pain. The clinician must remember that such unidimensional scales do not reflect a multidimensional problem.

Physical examination of patients with neuropathic pain

In general, all major parts of the physical examination are important for adequate determination of the presence of local disease that may cause pain. Any patient in whom the symptom characteristics suggest neurological origin may also demonstrate regional abnormalities of motor or reflex functions. However, the portions of the examination that are most relevant to the evaluation of neuropathic pain are those that are related to sensory dysfunction, such as hypoesthesia, hyperesthesia, hyperalgesia, and allodynia.

There are three important aspects in performing the sensory examination in patients with neuropathic pain: (a) the information that is obtained remains subjective, (b) stimulation with different modalities may create a mixed or uninterpretable response pattern, and (c) there may also be hypoesthesia or even areas of total anesthesia in the middle of areas that the patient describes as being so painful.

Techniques that should be utilized during the examination should include vibration perception threshold using a 128-Hz tuning fork (looks at large fibers), light touch sensation using Nylon Semmes Weintein mono-filaments or Von Frey hairs (for testing large myelinated Aα and Aβ fibers), thermal sensation thresholds mediated by the unmyelinated C fibers (warmth) and cold by the Aδ fibers. Autonomic function should be tested, looking at sudomotor function, blood pressure responses. It may also, in some cases, be advisable to perform skin punch biopsies with immunohistochemical staining looking for nerve fiber density, as well as decreased levels of substance P and CGRP particularly in diabetic neuropathy.

The severity of a pain condition can be related to the size of a painful area, but the intensity is independent of how large or small the territory.

Management and Treatment

Integration of history/physical data for neuropathic pain evaluation

It is evident that the duration and complexity of the clinical evaluation of human neuropathic pain (NP) is highly dependent upon the patient’s ability to tolerate long and potentially
uncomfortable functionality and procedures. For screening purposes, however, different methods have been developed to provide a combination of individual components of the history and physical examination. The more simple and direct methods are exemplified by Galer and Jensen and Krause and Backonja. Development of a neuropathic pain questionnaire demonstrates burning pain, shooting pain, numbness, electric pain, tingling pain, squeezing pain, freezing pain, and significant sensitivity to touch. Analysis of the elements reveals that the three most valuable features were the symptoms of numbness, tingling pain, and the mixed response of symptoms/signs expressed as increased pain due to touch on physical examination.

**Laboratory, radiologic, and electrodiagnostic assessment**

Once the history, physical findings, and neuropathic pain questionnaire have yielded sufficient evidence to support the potential presence of NP, specific biochemical, structural, and neurophysiological tests may be applied to confirm or eliminate certain disorders from the differential diagnosis.

Laboratory evaluation is necessary to determine the presence of hematologic, chemical, or pathophysiologic processes with a high potential for causing or contributing to the pain. Such tests are also used to monitor (a) systemic response to treatment since there are often effects on renal (Clcr) and hepatic function and (b) serum or urine levels of primary analgesics and certain adjuvant medications, such as some antidepressants and anticonvulsants. DNA and other specific biochemical tests for neuropathic pain disorders that have a familial tendency or pattern of inheritance can be helpful for genetic counseling, but are not often ordered in primary care pain practice. Similarly, direct and electron microscopic assessment of nerve tissue obtained at biopsy is only used selectively for the definitive pathological diagnosis of certain illnesses, such as neuropathy.

Radiologic evaluation provides valuable information about the presence or absence of structural lesions compressing or invading tissues of the brain, brainstem, spine, spinal cord, root, plexus, or nerve. Certain specialized tests are known to be helpful in the diagnostic assessment of specific conditions, e.g., triple-phase contrast bone scan as a tertiary way of testing for CRPS type I/RSD.

Electroneurodiagnostic tests are helpful in localizing structural lesions or regional dysfunction in many disorders of the nervous system, not just those related to neuropathic pain. However, common procedures such as electroencephalography and electromyography/nerve conduction studies to the medical assessment of painful conditions of the brain and spinal cord, root, and nerve, respectively, are known to be helpful in confirming and localizing many neurological illnesses presenting with pain. For painful disorders, such as CRPS types I and II, and sympathetically mediated or maintained pain (SMP), a wide range of electrophysiological tests of sympathetic sudomotor function can be found, including selective tissue conductance (STC) assessment of the skin over painful and nonpainful regions.

**Initial symptom management**

There is some disagreement as to which treatment approaches (pharmacotherapeutic or interventional) represent the best and worst chances for symptom control. Neither approach is mutually exclusive. Nevertheless, the mainstay of treatment of neuropathic pain is pharmacotherapeutic. Effective regimens often require multiple medications. The patient should be aware that pain will be less in quality and intensity and may not be ablated.

Attempts at monotherapy with standard analgesics including some opioids tend to be less effective, since neuropathic pain can be resistant to medications of that type. Opioids that have monoamine reuptake inhibition may offer some advantages (tramadol and tapentadol). Neuropathic pain may be treated with some success using adjuvant analgesics, i.e., medications not traditionally considered to be pain relievers. Adjuvant analgesics, such as...
TCAs, SNRIs, anticonvulsants, and others (baclofen, capsaicin, and lidocaine) do not have strong antinociceptive analgesic properties in experimental or clinical studies, but have been shown to be helpful in neuropathic pain states.\textsuperscript{234,235} In addition, the possible effectiveness of opioids for neuropathic pain should not be overlooked, although doses may cautiously be titrated and differ from those of typical antinociceptive doses.\textsuperscript{236}

The clinician should recall that successful management of chronic pain often requires treating neuropathic pain as well as pain associated with tissue injury, because both conditions may coexist and interact to maintain the painful condition. Chronic pain syndromes are often a product of integrated nociceptive and neuropathic mechanisms, and as such require consideration of both types for any pain lasting greater than 3–6 months. Nonsteroidal anti-inflammatory agents have no usefulness in neuropathic pain management but may have benefit with the other comorbid musculoskeletal pain conditions (Tables 3 and 4). The rare acetaminophen (APAP) risks include Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) that begin with flu-like symptoms followed by rash, skin blistering, and extensive skin surface damage/peeling. A third skin reaction, acute generalized exanthematous

| Table 3 |
| The non-NSAIDs analgesic |

<table>
<thead>
<tr>
<th>Acetaminophen (APAP)</th>
<th>1A2, 2A6, 2C9, 2D6, 2E1, and 3A4</th>
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<tr>
<td></td>
<td>3A4</td>
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| Table 4 |
| The nonsteroidal anti-inflammatory drugs (NSAIDS)\textsuperscript{237–239} |

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Metabolic substrate pathway</th>
<th>CYP450 inhibitor</th>
<th>PG category</th>
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</thead>
<tbody>
<tr>
<td>Acetic acid derivatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac (plus misoprostol)</td>
<td>3A4, misoprostol: rapid de-esterification to free acid</td>
<td>2C9, 3A4, and 2C8</td>
<td>X</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2C9, 2E1, and 3A</td>
<td></td>
<td></td>
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<tr>
<td>Etodolac</td>
<td>Hepatic</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2C9 and 2C19</td>
<td>2C9 and 2C19</td>
<td>C/D</td>
</tr>
<tr>
<td>Sulindac</td>
<td>Hepatic, prodrug (sulfide to sulfone)</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>Conjugation inactive metabolite</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Carboxylic acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (acetylsalicylic acid, ASA)</td>
<td>Gl mucosa, RBC, spinal fluid, and blood</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Buffered aspirin</td>
<td>Esterase</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Choline magnesium trisalicylate</td>
<td>Similar to above/ASA</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Saturable hepatic pathway to glucuronides</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Enteric-coated salicylates</td>
<td>Salicylate metabolism</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Hepatic conjugation</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Fenamates</td>
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<td></td>
</tr>
<tr>
<td>Etolic acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meclomenate hepatic</td>
<td>Hepatic</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Mefenamic</td>
<td>2C9</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>2C9 and 3A4</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>2C18 and 2C9</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Naphthylamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabumetone</td>
<td>Hepatic prodrug to 6 MNA extensive first pass</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Selective COX-2 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celecoxib (sulfonamide)</td>
<td>2C9, 3A4</td>
<td>2D6, 2C8</td>
<td>C/D</td>
</tr>
<tr>
<td>Etoracoxib</td>
<td>3A4</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>2C9</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Propionic acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>Extensive hepatic</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>2C9</td>
<td>2C9</td>
<td>C/D</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2C9 and 2C19</td>
<td>2C9</td>
<td>C/D</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Phase II, enterohepatic recirculation</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Naproxen, enteric</td>
<td>1A2 and 2C9</td>
<td></td>
<td>C/D</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>CYP oxidation</td>
<td></td>
<td>C/D</td>
</tr>
</tbody>
</table>
pustulosis (AGEP), resolves within 2 weeks of stepping the causative medication (FDA Consumer Health Information, Aug 2013).

**Mechanistic basis of neuropathic pain management**

Management of neuropathic pain is a complicated endeavor and often is frustrating to patient and physician alike. This stems from our relatively incomplete understanding of mechanisms and the limited efficacy of currently available analgesics. Therapeutic approaches vary greatly among physicians, which reflect the paucity of randomized clinical trials, particularly those comparing different recognized drug regimens. Given our current level of understanding of neuropathic pain mechanisms and the limitations of available pharmacotherapies, nonpharmacological (interventional) methods may be as effective as pharmacological approaches. Recalcitrant chronic pain syndromes warrant an interdisciplinary approach, which may include attempts to treat the underlying disease (e.g., causes of the peripheral neuropathy) as well as formulation of a rational titrated approach to medications, interventions such as nerve blocks, and psychological and physical therapies.

**Adjuvant analgesics: anticonvulsants, tricyclic antidepressants and SNRIs (Tables 6–8)**

It is often helpful to consider the various medications useful for neuropathic pain in terms of their traditional pharmacological indications (e.g., anticonvulsants and antidepressants). However, it is necessary to keep in mind that all these drugs have incompletely understood mechanisms of action, and the drug categories are more conventional than mechanistic.

**Table 5**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>PG risk factor</th>
<th>CYP substrate</th>
<th>CYP inducer (inducer)</th>
<th>Any active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>C</td>
<td>3A4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>C</td>
<td>3A4</td>
<td>1A2, 2A6, 2C19, and 2D6</td>
<td>Norbuprenorphine</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>C/D</td>
<td>2D6 and 3A4</td>
<td>2D6</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>C/D</td>
<td>2D6</td>
<td>2D6</td>
<td>Morphine</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>C/D</td>
<td>3A4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>C/D</td>
<td>2D6 and 3A4</td>
<td>3A4</td>
<td>Hydromorphone H-3G and H-6-G</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>C/D</td>
<td>Phase II glucuronidation conjugated 6-OH minor metabolites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>C/D</td>
<td>Phase II and 2D (minor)</td>
<td></td>
<td>Hydromorphone M-3-G and M-6-G</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>C/D</td>
<td>Hepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>C/D</td>
<td>2B6, 2C19, and 3A4</td>
<td>2D6 and 3A4</td>
<td>Normeperidine</td>
</tr>
<tr>
<td>Methadone</td>
<td>C/D</td>
<td>3A4, 2C9, 2C19, 2D6, and 2B6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>C/D</td>
<td>2D6 and 2D (minor)</td>
<td>2D6 and 3A4</td>
<td>M-3-G and M-6-G</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>C/D</td>
<td>Hepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>B/D</td>
<td>2D6 and 3A4</td>
<td></td>
<td>Oxyphene</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>C</td>
<td>Phase II glucuronidation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentazocine</td>
<td>C/D</td>
<td>Oxidation and glucuronidation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>C/D</td>
<td>2D6</td>
<td>2D6</td>
<td>Norpropoxyphene</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>C</td>
<td>Unknown CYP450 nonspecific esterases (blood) and tissue</td>
<td>2D6</td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>C</td>
<td>3A4 and hepatic small intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>C</td>
<td>2B6, 2D6, and 3A4</td>
<td></td>
<td>N-desmethyl-tramadol</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>C</td>
<td>Phase II = 15%, 2C9, 2D6, and 2C19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacology of neuropathic pain

From a practical standpoint, pharmacotherapy remains the pillar of pain management strategies, despite their limitations. From a conceptual standpoint, adjuvant analgesic drugs may be categorized into two broad classes, membrane-stabilizing agents (AEDs and anesthetics) and medications that enhance inhibitory mechanisms in the dorsal horn. This classification system may provide a simple framework with which to approach therapy; however, it should be kept in mind that most of these agents have multiple mechanisms of action, and their effects often may overlap. Given the limitations of our current medications, pain management often becomes a clinically based titration exercise in polypharmacy, where the clinician uses multiple pharmacotherapeutics to target different symptoms in a patient-specific, patient-focused, patient-centered, personalized care plan. This strategy may optimize the chances for success, but complicates management issues when side effects develop.

Mechanisms of action

Membrane-stabilizing agents include local anesthetics, such as lidocaine and some anticonvulsant drugs, including topiramate (TPM), carbamazepine (CBZ), phenytoin (PHT), and valproic acid (VPA). Their molecular mechanism of action involves blockade of frequency and voltage-dependent sodium channels on damaged or regenerating neuronal membranes. It appears that minimal doses of suppressive drugs may inhibit ectopic discharges without interfering with normal neuronal function. It is also possible that the sodium channel targets are atypical and not involved in normal neuronal conduction. Although the evidence is less substantial, corticosteroids also appear to have effects on membrane conductance. In addition, tricyclic antidepressants, such as amitriptyline, have effects on sodium channels, an action that is distinct from their effects on the reuptake of serotonin and norepinephrine. The latter are traditionally thought to be responsible for their effects on depression and pain.

Conventional wisdom maintains that the adjuvant analgesics, particularly the tricyclic antidepressants, clonazepam, and baclofen, modulate inhibitory mechanisms in the spinal cord and brain. Inhibitory pathways descend from the periaqueductal gray, reticular formation, and

Table 6
Other agents with a disease-state specific analgesic indication

<table>
<thead>
<tr>
<th>Other analgesics</th>
<th>PG risk factor</th>
<th>Substrate</th>
<th>CYP inducer</th>
<th>CYP inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>C</td>
<td>1A2, 2D6</td>
<td>IA2</td>
<td>1A2, 2D6</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>C</td>
<td>Almost not metabolized</td>
<td>IA2</td>
<td>1A2, 2D6</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>C</td>
<td>Almost not metabolized</td>
<td>IA2</td>
<td>1A2, 2D6</td>
</tr>
</tbody>
</table>

Table 7
Anticonvulsants—mood stabilizers

<table>
<thead>
<tr>
<th>Agent</th>
<th>PG risk factor</th>
<th>CYP substrate</th>
<th>CYP inhibitor (inducer)</th>
<th>Any active metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>D</td>
<td>3A4, 2C19, 2C9, 3A4, and 2E1</td>
<td>Autoinduction 5 weeks Inducer 2B6, 2C19, 3A4, 2C9, and 2C8</td>
<td>Epoxide metabolite</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>D</td>
<td>2A6 and 2B6</td>
<td>2C9 inducer and 2A6</td>
<td>--</td>
</tr>
<tr>
<td>Valproate</td>
<td>X</td>
<td>3A4 (phase II glucuronidation and sulfation)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>D</td>
<td>Phase II hydroxylation and deamination</td>
<td>2C19 (induces 3A4)</td>
<td>--</td>
</tr>
<tr>
<td>Topiramate</td>
<td>D</td>
<td>Phase II glucuronidation</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>C</td>
<td>Phase II</td>
<td>3A4 (inducer)</td>
<td>MHD</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>C</td>
<td>Phase II</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Levotiracetam</td>
<td>C</td>
<td>Phase II</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
nucleus raphe magnus in the dorsolateral funiculus to the dorsal horn. These pathways mediate antinociception by adrenergic, serotonergic, gamma-aminobutyric acid (GABAergic), and opioid mechanisms. Although the putative mechanisms are complex and poorly understood, serotonergic effects are mediated in part by action on GABAergic interneurons. For example, facilitatory effects of large myelinated afferent fibers may be suppressed by tonic GABAergic activity, removal of which results in allodynia.

As noted earlier, tricyclic antidepressants alter monoamine transmitter activity at neuronal synapses by blocking presynaptic reuptake of norepinephrine and serotonin, thereby modulating descending inhibitory spinal pathways. However, additional mechanisms include effects on membranes, interaction with NMDA activity, and sodium channel blockade.

The treatment of comorbid depression and anxiety

It is crucial that psychosocial and emotional factors be anticipated and clinically explored, because there is a high comorbidity of depression and anxiety disorders in patients with chronic pain. Moreover, given the similarities between the pharmacology of mood and depression and pain transmission (e.g., serotonin and norepinephrine), patients with concomitant systemic illness and stress may be at risk for depression and development of an abnormal chronic pain state. Pharmacotherapeutic management of depression may improve neuropathic pain by addressing overlapping, but distinct mechanisms.

Ablative procedures

After multiple therapeutic medication trials in which there has been minimal patient-perceived therapeutic benefit and perhaps significant drug-related side effects, patients may believe that they have little recourse but to undergo invasive, ablative procedures in attempts to relieve their pain. Specific treatment modalities aimed at the underlying pathophysiology are usually not possible in most neuropathies, particularly with chronic sensory polyneuropathies. In general, ablative procedures are not warranted, because of the high probability of long-term worsening of pain. Except for patients with advanced cancer-related pain, nerve ablation is likely to provide only temporary benefit, leaving the patient with sensory and perhaps motor deficits. Exceptions to this phenomenon appear to be ablation of sympathetic fibers, visceral plexi, and medial branch nerve blocks, which denervate painful facet joints in the spine. In cases of nerve entrapment, where ongoing nerve compression is likely to be responsible for pain, neurolysis or
transposition of the nerve may provide benefit, as long as pain is not due to irreversible underlying nerve damage. In all cases of neuropathic pain, even when neuropathy is evident, it is appropriate from time to time to reevaluate the presumed etiology of the neurological problem. Patient-perceived beneficial expectations of treatment outcomes must be negotiated against the reality of titration and therapeutic outcome.

When a medication trial proves to be ineffective, a multidimensional or interdisciplinary approach should be considered. Again, this includes an attempt to treat the underlying disease, as well as specific pharmacological, psychological, and physical therapy interventions. The outcome measure for successful treatment should include increased activity as well as decreased subjective pain ratings and improved patient satisfaction. The treatment goal in chronic neuropathic pain is different from that in acute pain. In the usual acute pain setting, the goal is nearly complete relief of pain to allow recovery of normal function during the healing process. With chronic neuropathic pain, limitations of current analgesics usually make complete pain relief a very unrealistic goal. Therefore, attention to increasing functions and comfort and treating associated problems, such as depression, becomes paramount. Reducing dependence on opioid medications may or may not be an important treatment plan/goal. The objectives to consider with chronic opioid therapy include determining whether nonopioid approaches have been given an appropriate therapeutic trial, whether the pain syndrome is opioid responsive, and whether the patient demonstrates appropriate improvement in functionality; increased activity of daily living; vocational and avocational pursuits; without undue side effects; or evidence of abuse, misuse, or diversion of medications.

Nonpharmacological approaches to treating neuropathic pain include the use of a TENS unit, although relief may be poor when burning pain is a prominent complaint. This may be explained by the fact that burning pain is a C-fiber-mediated sensation, whereas TENS units probably modulate large-fiber input into the dorsal horn.

Spinal cord stimulation may be efficacious for chronic pain, including neuropathic pain and complex regional pain syndrome/reflex sympathetic dystrophy. Mechanisms involved are poorly understood, which reflects current understanding of neuropathic pain states in general. However, central effects may include alteration in dorsal horn processing and transmission in the tract of Lissauer and suppression of sympathetic outflow from the intermediolateral gray column of the spinal cord. The latter effect may explain improved peripheral blood flow in patients with chronic peripheral vascular insufficiency. The Craig PENS technique, a novel application of electroacupuncture [percutaneous neural stimulation (PNS)] has been shown to be effective in herpes zoster, diabetic peripheral neuropathy, and sciatica.

Available evidence indicates that nonpharmacological approaches, such as TENS and Craig PENS, can provide an initial rational therapeutic strategy and may obviate the need for potentially toxic medications, improve the effectiveness of current analgesic regimens, or reduce the amount of medications required. Spinal cord stimulation still tends to be a treatment of last resort, although judicious use earlier in the course of treatment is probably warranted in carefully selected patients. Considering the availability to the patient, current high cost and co-pays of medication, alternative approaches, if efficacious, may prove to be cost effective.

A peculiar property of the nervous system is its plasticity. Damage to nerves often results in alteration or amplification of the signal encoded by the nerve. For example, peripheral nerve ablation, performed with good therapeutic intentions, may result in a pain syndrome that is worse than the one originally being treated. When dealing with the nervous system, “shooting the messenger” (the nerve) often intensifies and distorts the message. The new pain syndrome may be more severe and associated with allodynia, hyperalgesia, and spontaneous and paroxysmal pain, all in the presence of mild to moderate cutaneous numbness. This complex of signs and symptoms is paradoxical to the patient and confusing to the clinician, but quite typical of neuropathic pain.

Mechanistic approach to the selection of treatment

When standard therapies are found to be only partially effective in controlling symptoms it is often helpful to select other medications or interventions based upon the compatibility of the
mechanisms of the patient-specific illness and the treatment being considered\textsuperscript{260} (Boswell et al., 1991).

For example, it has become popular to contrast neuropathic pain with typical postinjury, nociceptive pain. Nociceptive pain, typically thought to indicate a properly functioning nervous system, is considered physiological because it results from activation of nociceptors, specialized nerve endings that respond to high threshold noxious stimuli and generally serve a protective function.

In contrast, neuropathic pain may be thought of as pathophysiological, because it arises from a damaged PNS or CNS and provides no obvious protective benefit.\textsuperscript{2,12}

On the other hand, pain associated with peripheral neuropathy may be maintained by sustained peripheral nociceptive input.\textsuperscript{261} Strong nociceptive input often produces central sensitization, an abnormal pain amplification process in the CNS. Therefore, the definitional borders of neuropathic pain are becoming more diffuse, not more distinct, as we gain a better understanding of the remarkable plasticity of the nervous system and its close association with the various tissues that it innervates.

Neuropathic pain may also be classified as stimulus-evoked or stimulus-independent pain. Stimulus-evoked pain can result from stimulation of nervi nervorum present in connective tissue surrounding otherwise intact nerves. Painful stimuli that activate nociceptors around nerves include inflammation and tissue injury from tumor or trauma.\textsuperscript{172}

Stimulus-independent neuropathic pain may result from damage to afferent sensory fibers in the PNS or CNS. In this case, ongoing inflammation is usually absent. Days to months after peripheral nerve injury, persistent abnormal primary afferent activity from the periphery may arise from hypersensitive nerve terminals or nerves.\textsuperscript{262}

**Stimulus-evoked neuropathic pain and opioid analgesics**

Various studies suggest that stimulus-evoked neuropathic pain is more sensitive to selected opioids than stimulus-independent pain.\textsuperscript{229} Opioid responsiveness may be maintained in some forms of stimulus-evoked pain, because opioid receptors in the substantia gelatinosa are preserved. On the other hand, segmental loss of presynaptic central opioid receptors occurs following injury or loss of C fibers, typically seen after deafferentation injury. However, the magnitude of receptor loss is minimal and largely segmental, and only partly explains the diminished opioid responsiveness characteristic of neuropathic pain.\textsuperscript{174}

Supraspinal facilitative mechanisms may also be involved in maintenance of neuropathic pain and opioid resistance. Evidence suggests that sustained afferent drive induces facilitation of spinal cord pain transmission involving a descending pathway from the rostroventral medial medulla (RVM).\textsuperscript{174} Tonic facilitation may involve supraspinal choleystokinin (CCK), traditionally thought of as a visceral hormone that regulates emptying of the gall bladder. CCK antagonists injected into the RVM in animals reverse tactile and thermal allodynia produced by spinal nerve ligation.\textsuperscript{263} Mechanistically, these antinociceptive and pronociceptive actions may occur at spinal and supraspinal sites. Spinal CCK may antagonize opioid effects at the level of the primary afferent terminal in the spinal cord. Both CCK and opioids colocalize on primary nociceptive afferent neurons in the dorsal horn. In addition, CCK may act on supraspinal opioid-dependent pathways in the RVM to reduce opioid responsiveness and thus impair descending inhibition, an important mechanism involved in opioid pain relief. Ultimately, CCK antagonists may prove useful for treating neuropathic pain states.

The phenomenon of reduced opioid responsiveness in neuropathic pain has prompted extensive studies in animals, particularly the effects of intrathecal opioids on pain associated with thermal and tactile stimulation. The similarities between opioid tolerance and neuropathic pain are also an area of active study.\textsuperscript{264} It is well known that N-methyl-d-aspartate (NMDA) antagonists (ketamine, methadone, acetaminophen, orphendrine, tramadol, etc.) appear to minimize the development of opioid tolerance. Spinal dynorphin may be a common link between NMDA, central sensitization, and reduced opioid responsiveness. Following spinal
nerve ligation, dynorphin levels in the spinal cord increase, suggesting that dynorphin may act as a pronociception mediator.\(^{174}\) Although, under certain circumstances, dynorphin appears to have analgesic properties, it is becoming increasingly clear that dynorphin also has nonopioid, antianalgesic properties. Antiserum to dynorphin blocks thermal hyperalgesia after nerve injury in rats. Moreover, antiserum to dynorphin or MK801, an NMDA antagonist, restores normal spinal morphine analgesia following spinal nerve ligation. Furthermore, both agents restore morphine synergy between the brain and spinal cord,\(^{174}\) which is required for the full clinical analgesic effects of morphine. Therefore, current evidence suggests that the pain-promoting effect of dynorphin is mediated by the NMDA receptor. Although the full clinical ramifications of dynorphin are far from understood, it is clear that sustained nociceptive drive from the periphery maintains elevated levels of spinal dynorphin, which in turn, may have toxic effects on the spinal cord. Thus, reducing sustained peripheral nociceptive input into the spinal (i.e., pain relief) may be an important way to reduce the incidence of neuropathic pain.\(^{265}\)

Currently, NMDA antagonists, such as parenterally and orally administered ketamine, have evolving indications with some predictable significant side effects. Ultimately, however, newer, oral medications such as NMDA antagonists may become available that can reduce the effects of pathological spinal dynorphin\(^{237-239,266}\) (Table 5).

### Anticonvulsants\(^{237-239}\) (Table 7)

Anticonvulsants are useful for trigeminal neuralgia, postherpetic neuralgia, diabetic neuropathy, and central pain.\(^{233,235}\) Although anticonvulsants have traditionally been thought of as most useful for lancinating pain, they may also relieve burning dysesthesias. Chemically, anticonvulsants are a diverse group of drugs, are typically highly protein bound, and undergo extensive hepatic metabolism. Carbamazepine (CBZ) has a long history of use for neuropathic pain, particularly trigeminal neuralgia. Trigeminal neuralgia is an FDA-approved indication for the drug. Carbamazepine is chemically related to the tricyclic antidepressant, imipramine, has a slow and erratic absorption, displaying autoinduction, and may produce numerous side effects, including sedation, nausea, vomiting, and hepatic enzyme induction. In 10% of patients, transient leukopenia and thrombocytopenia may occur, and in 2% of patients hematologic changes can be persistent, requiring stopping the drug.\(^{267-269}\) Aplastic anemia is the most severe complication associated with carbamazepine, which may occur in 1:200,000 patients. Although requirements for hematologic monitoring remain debatable, a complete blood cell count, hepatic enzymes, blood urea nitrogen (BUN), and creatinine are recommended at baseline; and these are checked again at 2, 4, and 6 weeks, and every 6 months thereafter. Carbamazepine levels should be drawn every 6 months and after changing the dose to monitor for toxic levels and verify that the drug is within the therapeutic range (4–12 mg/ml). Patients with low pretreatment white blood cell counts are at increased risk of developing leukopenia (WBC < 3000/mm\(^3\)). Because toxicity is entirely unpredictable, it is important to instruct patients to recognize clinical signs and symptoms of hematologic toxicity, such as infections, fatigue, ecchymosis, and abnormal bleeding, and to notify the physician if they develop. To improve compliance, carbamazepine should be started at a low dose (e.g., 50 mg twice daily or less) and increased slowly over several weeks to a therapeutic level (200–300 mg four times a day).

Phenytoin (PHT) also has well-known sodium channel-blocking effects and is useful for neuropathic pain.\(^{239}\) However, it is less effective than carbamazepine for trigeminal neuralgia.\(^{270}\) We have also noted that neuropathic pain caused by structural lesions causing nerve or root compression can paradoxically increase when phenytoin is administered. Phenytoin has a slow and variable oral absorption, some of which is dependent upon GI motility and transit time. Toxicity includes CNS effects and cardiac conduction abnormalities. Side effects are common and include hirsutism, gastrointestinal and hematologic effects, and gingival hyperplasia.\(^{271}\) Allergies to phenytoin are common and may involve the skin, liver, and bone marrow. Phenytoin doses in the range of 100 mg twice or three times a day may be helpful for neuropathic pain; therapeutic blood levels are in the range of 10–20 mg/ml. There are numerous
potential drug interactions, including induction of cytochrome P450 enzymes, which may accelerate the metabolism of other drugs. Because of side effects and toxicity, phenytoin is not a first-line drug for neuropathic pain.

Valproic acid (VPA) appears to interact with sodium channels but may also alter GABA metabolism. The principle non-antiepileptic FDA-approved use of valproic acid is for the prophylaxis of migraine headache. Potential precautions, warnings, and toxicity include hepatotoxicity, pancreatitis, thrombocytopenia, hyperammonemia, fetal risk, hypothermia, and hypersensitivity reactions.

Divalproex sodium is better tolerated than valproic acid. The recommended starting dose is 250 mg twice daily, although some patients may benefit from doses up to 1000 mg/day. As a prophylactic drug, valproic acid can reduce the frequency of migraine attacks by about 50%. Although there is little published information on the efficacy of valproic acid for neuropathic pain syndromes, based on its mechanism of action it may be useful alone or in combination with other adjuvant drugs.

Clonazepam (CLZM) may be useful for radiculopathic pain and neuropathic pain of a lancinating character. Clonazepam enhances dorsal horn inhibition by a GABAergic mechanism. The drug has a long half-life (18–50 h), which reduces the risk of inducing an abstinence syndrome on abrupt withdrawal. The major side effects of clonazepam include sedation and cognitive dysfunction, especially in the elderly. Although the risk of organ toxicity is minimal, some clinicians recommend periodic complete blood count (CBC) and liver function tests for monitoring. Starting doses of 0.5–1.0 mg at bedtime are appropriate to reduce the incidence of daytime sedation.

Topiramate (TPM) was found to be identical to placebo in three placebo-controlled trials for painful diabetic neuropathy, while a fourth, independent placebo-controlled trial used different methods to assess topiramate efficacy and tolerability. It was found that in this one study topiramate monotherapy reduced pain and body weight more effectively than the placebo. Word-finding events, renal stones (calcium phosphate), weight loss, and visual effects have been reported.

Gabapentin is an anticonvulsant gabapentinoid, which has been used for neuropathic pain and restless-legs syndrome (RLS) and PHN. Gabapentin was released for use in the United States in 1994, for the treatment of adults with partial epilepsy. Following its release, prescribers began to use gabapentin for various “off-label” neuropathic pain disorders, such as diabetic peripheral neuropathy, neuropathic pain, and postherpetic neuralgia (PHN). The affinity to the α2delta subunit on the calcium channel has an unknown effect to the therapeutic effects. Absorption of gabapentanoids may include active transport mechanisms by proton-linked monocarboxylate transporter (MCT-1) found within the intestinal tract. Active renal excretion is through an organic cation transporter within renal sites. The $T_{1/2}\beta$ is 5–6 h. Hemodialysis removes gabapentin. Gabapentinoids do not appear to involve CYP450 induction or inhibition and is not a substrate or inhibitor of P-glycoproteins. Gabapentin bioavailability (F) is inversely proportional to dose as a function of saturation.

Although tricyclic antidepressants have been proven clinically effective for neuropathic pain for years, they often fail to provide adequate pain relief or initiate patient-specific unacceptable side effects. Therefore, when gabapentin became available, its more benign side effect profile made it desirable among prescribers. Although initial enthusiasm for the drug was based largely on word of mouth, anecdotal published reports, and discussions at clinical meetings, animal studies have substantiated the efficacy of gabapentin in various types of neuropathic pain. Over time, a growing consensus concerning the usefulness of gabapentin has emerged.

It is clear that gabapentin is not a direct GABA agonist, although indirect effects on GABA metabolism or action may occur. A leading hypothesis suggests that gabapentin interacts with a novel receptor on a voltage-activated calcium channel. Research has shown that it interacts with the α2delta subunit on the voltage-gated calcium channel. Inhibition of voltage-gated sodium channel activity (such as occurs with classical anticonvulsants, e.g., phenytoin and carbamazepine) and amino acid transport, which alters neurotransmitter synthesis, may also occur. Although gabapentin is not an NMDA antagonist, there is evidence that gabapentin interacts with the glycine site on the NMDA receptor.
The affinity to the α2delta subunit on the calcium channel has an unknown effect to the therapeutic effects. Absorption of gabapentinoids may include active transport mechanisms by proton-linked monocarboxylate transporter (MCT-1) found within the intestinal tract; active renal excretion is through an organic cation transporter within renal sites. The $T_{1/2}$ is 5–6 h. Hemodialysis removes gabapentin. Gabapentinoids do not appear to involve CYP450 induction or inhibition and is not a substrate or inhibitor of P-glycoproteins. Gabapentin bioavailability is inversely proportional to dose as a function of saturation.

Ligation of rat spinal nerves, L5 and L6 (the Chung model), produces characteristic pain behaviors, including allodynia, which are typical of neuropathic pain. Chapman et al.\(^{276}\) demonstrated that gabapentin reduces pain in the Chung model. Gabapentin appears to act primarily in the CNS, in contrast to amitriptyline, which seems to act centrally and peripherally.\(^{277}\) Gabapentin also is effective in reducing pain behavior in phase 2 of the formalin test, a model of central sensitization and neuropathic pain.\(^{278}\) Gabapentin reduces spinally mediated hyperalgesia seen after sustained nociceptive afferent input caused by peripheral tissue injury. Gabapentin also enhances spinal morphine analgesia in the rat tail-flick test, a laboratory model of nociceptive pain.\(^{279}\)

Gabapentin is effective in reducing painful dysesthesias and improving quality of life scores in patients with painful diabetic peripheral neuropathy.\(^{280}\) Of patients randomized to receive gabapentin, 56% achieved a daily dosage of 3600 mg divided into three doses per day. The average magnitude of the analgesic response was modest, with a 24% reduction in intensity at the completion of the study compared with controls. Side effects were common. Dizziness and somnolence/sedation occurred in about 25% of patients and confusion occurred in 8% of patients.

Morello et al.\(^{281}\) compared gabapentin with amitriptyline for diabetic neuropathy and found both equally effective. However, the NNT for the tricyclic antidepressants is 2.5 and 4.2 for gabapentin.\(^{282–284}\) Although gabapentin probably has fewer contraindications than tricyclic antidepressants, both drugs have a labeled caution for suicidal ideation or behavior. Recall as the dose increases, the absorption of gabapentin decreases. The dose is also a function of creatinine clearance (CLcr) in all patients.

Postherpetic neuralgia (PHN) is another difficult neuropathic syndrome. PHN affects approximately 10–15% of patients who develop herpes zoster and is a particularly painful syndrome associated with lancinating pain and burning dysesthesias. The incidence of PHN is age related, with up to 50% of patients older than 60 years of age developing persistent pain after a bout of herpes zoster.\(^{285}\) Pain relief usually requires pharmacological therapy. Unfortunately, most medications are not very effective. For example, only about one-half of patients obtain adequate relief with antidepressants. An animal model has demonstrated alldynia. Rowbotham et al.\(^{286}\) evaluated the efficacy of gabapentin for the treatment of PHN. Of patients taking gabapentin, 65% achieved a daily dosage of 3600 mg. Although the average magnitude of pain reduction with gabapentin was modest, with an approximately 30% reduction in pain compared with controls, statistically pain reduction was highly significant. In addition, gabapentin improved sleep parameters and quality of life scores. Adverse effects that occurred more commonly in the gabapentin group included somnolence (27%), dizziness (24%), ataxia, peripheral edema, and infection (7–10%). Postmarketing events include breast enlargement, gynecomastia, and elevated creatine kinase. Based on the data of Rowbotham et al., it is reasonable to consider gabapentin as firstline therapy for postherpetic neuralgia. Gabapentin probably is at least as effective as antidepressants, with fewer contraindications. Gabapentin may be used as monotherapy or add-on treatment.

Although gabapentin can theoretically be started at 300 mg three times a day with most patients, it has been the clinical experience of the authors that initiating lower initial doses (100 mg) with cautious and slow escalation of the drug up to a schedule of four times a day (three times a day with meals and again at bedtime) has improved compliance. Use of the bedtime dose may assist with sleep and reduces nocturnal pain. In addition, this reduces the risk of patients stopping the drug because of side effects, before a therapeutic dose (i.e., 25 mg/kg ideal body weight per day) is achieved. In our experience, the most effective therapeutic schedule involves starting with a bedtime dose of 100 mg for 2 days. The daily dose is then
increased to 100 mg twice a day with breakfast and supper or breakfast and at bedtime for 2 days. Thereafter, the dose can be increased to three times a day with meals and at bedtime. Further titration every 3–7 days can be continued until subjective pain relief described by the patient, side effects, or a maximum daily dose in the range of 2400–3600 mg/day is reached. An instruction sheet for the patients is helpful in clarifying the dosage schedule. Slow tapering is needed to minimize potential withdrawal seizures.

Gabapentin is generally well tolerated, even in the geriatric population, considering CLcr and has a safer side effect profile than tricyclic antidepressants. In the PHN study, the majority of patients were titrated to 3600 mg/day, and the median patient age was 73 years. The kidneys excrete almost all gabapentin as the parent compound, and the dosage must be reduced for patients with renal insufficiency.287 Age-related decrements in renal function often decreases the clearance of pharmacotherapies (e.g., gabapentinoids) necessitating dose reductions.

Pregabalin is also a GABA analog, with similar structure and function to gabapentin. As a new class of anticonvulsants was named, the “gabapentinoids,” of which these two drugs are the first known for inclusion. Pregabalin is indicated for the treatment of neuropathic pain associated with both diabetic neuropathy and postherpetic neuralgia.237–239,288

Pregabalin, as with gabapentin, has negligible hepatic metabolism; it is not protein bound and has a plasma half-life of about 6 h. Most of the oral dose (95%) is found unchanged in the urine. Peak plasma levels are found in about 1 h postoral doses; oral bioavailability is about 90%.

Pregabalin binds to the α2delta subunit protein of the voltage-gated calcium channels, like gabapentin, and therefore reduces release of excitatory neurotransmitters.289

Several randomized clinical trials show pregabalin to be superior to placebo in the treatment of neuropathic pain (PHN and DPN) at doses of 300–600 mg/day. Sleep was improved. Common adverse events included dizziness, peripheral edema, weight gain, and somnolence.289 Thrombocytopenia, QTc prolongation, and cognitive events have also been described.

Randomized controlled studies of pregabalin in painful diabetic peripheral neuropathy were also done and showed the drug to be superior to placebo in doses of 300–600 mg/day. Improvements in sleep were also seen.290–293

Pregabalin was also evaluated for use in Canada for the treatment of peripheral neuropathic pain. The past treatment was reviewed. It was noted that the number of subjects with > 50% reduction in pain was increased when pregabalin was compared to placebo. Withdrawal due to adverse events was more frequent with pregabalin than placebo. The authors concluded that while pregabalin appeared effective in the treatment of peripheral neuropathic pain, no evidence was found that it offered advantages over the treatments currently being used in Canada.294

Antidepressants235,236,237 (Table 8)

Tricyclic antidepressants have been used for years for the management of neuropathic pain syndromes, including diabetic neuropathy, postherpetic neuralgia, and migraine headache.234,295,296 However, pain relief is often modest and accompanied by side effects. Controlled studies indicate that approximately one-third of patients will obtain more than 50% pain relief, one-third will have minor adverse reactions, and 4% will discontinue the antidepressant because of major side effects.234 Fortunately, some patients achieve excellent pain relief.

Because comparisons between tricyclic antidepressants have not shown great differences in efficacy,234,295 the choice of which antidepressant to use often depends on patient pharmacokinetics and the medication medical pharmacodynamic profile of a given drug. For example, when a patient is having difficulty sleeping because of pain, a more sedating drug, such as amitriptyline, may be indicated. On the other hand, desipramine, which is less sedating, may be better tolerated in elderly patients.

The tricyclic antidepressants are generally highly protein bound with large volumes of distribution and long elimination half-lives. They undergo extensive hepatic first-pass metabolism and typically have active metabolites. Although effective doses may be lower than
typically used for depression, this is often not the case. Patients must be warned of potential side effects including sedation, cognitive changes, and orthostatic hypotension from \(\alpha\)-adrenergic blockade. Anticholinergic side effects are common and include constipation, urinary retention, visual blurring, and exacerbation of glaucoma. Antihistaminic effects may cause sedation. Because of their long half-lives, these drugs may be given as a single bedtime dose. To minimize side effects, small doses (e.g., 10–25 mg) are used initially and increased over several weeks to a therapeutic dose, generally in the range of 50–150 mg/day. An electrocardiogram (ECG) is recommended if there is a history of cardiac disease. ECG changes such as QRS widening, PR and QT prolongation, and T-wave flattening can be induced by these agents. Tricyclic antidepressants may have quinidine-like actions, consistent with their sodium channel-blocking effects, particularly in patients with underlying ischemic cardiac disease or arrhythmias.²⁹⁷ Because abrupt discontinuation of antidepressants may precipitate withdrawal symptoms, such as insomnia, restlessness, and vivid dreams, a gradual taper over 5–10 days is recommended. Occasional blood levels are recommended, as well as CBC and hepatic studies to monitor for organ toxicity.

Amitriptyline is a tertiary amine that inhibits norepinephrine and serotonin reuptake equally.²⁹⁸ Amitriptyline is probably the most commonly used tricyclic agent for neuropathic pain. Amitriptyline also is the most sedating of the tricyclic antidepressants and has the most potent anticholinergic effects. A starting dose of 25 mg at bedtime is recommended.

Amitriptyline is metabolized into nortriptyline, a secondary amine with twice as much inhibition of norepinephrine reuptake, compared with serotonin. Nortriptyline is less sedating than amitriptyline with less anticholinergic side effects. A starting dose of 10 mg at bedtime is generally well tolerated.

Imipramine is a tertiary amine with equal inhibition of norepinephrine and serotonin uptake. This drug is moderately sedating and has average anticholinergic effects. The suggested starting dose is 25 mg at bedtime. Because of unpredictable metabolism, occasional blood levels are suggested. Imipramine is metabolized to a secondary amine, desipramine, which is a much more selective inhibitor of norepinephrine uptake. Desipramine is less sedating and has fewer anticholinergic effects than imipramine or amitriptyline, is at least as effective for pain control, and is better tolerated by elderly patients.

Compared with tricyclic agents and SNRIs, serotonin–selective reuptake inhibitors (SSRIs) for neuropathic pain have been disappointing. In addition, they are more expensive than the older generic agents. Nonetheless, at relatively high doses (e.g., 60 mg), paroxetine is effective for diabetic neuropathy.²⁹⁹ Fluoxetine may also be useful in the treatment of rheumatic pain conditions, many of which have neuropathic components.³⁰⁰ SSRIs are better tolerated than tricyclic antidepressants and should be considered as firstline drugs in patients with concomitant depression. In this group, they may serve double duty.

Venlafaxine is a phenylethylamine antidepressant chemically distinct from the older tricyclic antidepressants and the serotonin-selective uptake inhibitors.²⁵¹ Although venlafaxine blocks serotonin and norepinephrine reuptake, its analgesic actions may be mediated by both an opioid mechanism and adrenergic effects.³⁰¹ The drug may be at least as well tolerated as tricyclic agents and more effective for pain than standard doses of serotonin-selective drugs. Indeed, an initial report suggests that venlafaxine is effective for neuropathic pain.³⁰² Venlafaxine should be started at one-half of a 37.5-mg tablet twice daily and titrated weekly to a maximum of 75 mg, taken twice a day. Nausea appears to be the most common side effect. An extended release formulation of the drug was effective in relieving the pain associated with diabetic neuropathy. The number needed to treat (NNT) values for the higher dose of venlafaxine ER are comparable with those of the TCAs and gabapentin.³⁰³ Duloxetine is a serotonergic and noradrenergic reuptake inhibitor with low affinity for other neurotransmitter systems. The most common adverse events are referable to the gastrointestinal and nervous systems. The FDA-approved pain indications include DPN, FMS, and chronic musculoskeletal pain. Duloxetine is primarily eliminated renally following significant hepatic metabolism via multiple oxidative pathways, methylation, and conjugation. The half-life is 12.1 h. Duloxetine does cause inhibition of CYP2D6. It should not be used in combination with
nonselective monoamine oxidase inhibitors or CYP 1A2 inhibitors.\textsuperscript{304} It is effective additionally and FDA approved for major depressive disorders and anxiety.\textsuperscript{305–307}

Several double-blind, randomized multicenter trials comparing duloxetine to placebo for the treatment of diabetic peripheral neuropathy have been done. In one, patients received duloxetine 60 mg daily, twice a day or placebo. Duloxetine was superior to placebo in both dosages; discontinuations secondary to adverse events were more frequent in the duloxetine 60-mg bid group.\textsuperscript{308}

In the second, a 12-week double-blind, placebo-controlled study in types 1 and 2 diabetics with painful diabetic neuropathy, both 60- and 120-mg/day dosages demonstrated statistically significant improvement in pain compared to placebo.\textsuperscript{309}

Duloxetine has also been found to be an effective and safe treatment for many symptoms associated with fibromyalgia in subjects with or without a major depressive disorder, particularly for women, who had the best outcomes, with significant improvement over most outcome measures.\textsuperscript{306,310,311}

Antidepressant drugs (ADMs) have been used for many years in the treatment of neuropathic pain. Reasons include the traditional monoaminergic hypothesis. It is also known that antidepressants can interfere with the opioid system, inhibit ion channel activity, and interact with the N-methyl-d-aspartate (NMDA) receptors. The tricyclic antidepressants (TCAs) have the lowest number needed to treat (NNT—the number of patients that need to be treated to achieve a 50\% decrement in pain in one patient). The NNT for TCAs is 2.4 vs. 6.7 for the selective serotonin reuptake inhibitors. It appears that the ADMs with noradrenergic reuptake inhibition in addition to serotonergic reuptake inhibition, such as venlafaxine and duloxetine demonstrate a better analgesic effect. The TCAs remain the first-choice treatment for neuropathic pain.\textsuperscript{86,312} However, no head-to-head comparisons between ADMs and other analgesics have been done.\textsuperscript{86,230,237–239,247–249,313,314}

**Opioids (Table 9)**

**Tramadol\textsuperscript{230–232,248}**

Tramadol appears to be a global utilized analgesic for chronic non-cancer pain of all types available in multiple dosage forums.

Tramadol is a centrally acting opioid analgesic that is related structurally to codeine and morphine. It consists of two enantiomers, both of which are important in the drugs’ analgesic mechanisms. The (+)-tramadol and the metabolite (+)-O-desmethyl-tramadol (also called M1)
are μ opioid receptor agonists. (+)-Tramadol also inhibits serotonin reuptake, while the
(−)-tramadol enantiomers inhibits norepinephrine reuptake, enhancing inhibitory effects on
spinal cord pain transmission.\textsuperscript{315}

Tramadol is rapidly absorbed after oral administration, some with action as a NMDA receptor
antagonist. It is rapidly distributed in the plasma, with about 20% plasma protein binding. It is
metabolized by O- and N-demethylation and by conjugation forming glucuronides and sulfates.
Tramadol and its metabolites are excreted mainly by the kidneys, with a mean elimination half-
life of about 6 h.\textsuperscript{282,315}

The O-demethylation of the drug to M1 is catalyzed by cytochrome P450 (CYP)\textsuperscript{282} CYP2D6,
2B6, and CYP3A4.

The analgesic potency of tramadol is only 10% of that of morphine status-post parenteral
administration. Tramadol produces less constipation and problems with dependence than
equianalgesic dosages of opioids.\textsuperscript{282} There are no respiratory or cardiovascular problems
associated with the drug.\textsuperscript{316}

M1 has a greater affinity to the μ receptor and is felt to be mainly responsible for tramadol
opiate activity.\textsuperscript{315}

It is felt that the dual activity (opioid and nonopioid) explains its effectiveness in pain that
may not be responsive to opioids alone: neuropathic pain.\textsuperscript{317}

Tramadol is among an initial choice opioid drug for the treatment of neuropathic pain; it has
been shown to be effective in several placebo-controlled studies.\textsuperscript{87,317–322}

In a Cochrane evidence-based review, tramadol was found to be “an effective treatment for
neuropathic pain.”\textsuperscript{323} The reviewers found five “eligible” RCTs, three comparing tramadol with
placebo, one comparing tramadol with clomipramine and one comparing tramadol with
morphine. All three trials comparing tramadol to placebo were positive, with tramadol being
superior to placebo. There was not enough evidence to develop a conclusion regarding tramadol
vs. morphine or clomipramine.\textsuperscript{323} It was determined that the NNT was 3.5 (the number needed
to treat, to find one patient with a greater than 50% diminution of pain).\textsuperscript{323,324}

For moderate to severe pain, start at 2 mg PO qam, then increase by 25 mg/day every 3 days
to 25 mg qid, then increase by 50 mg/day every 3 days to 50 mg qid. Maximum dosage should
not exceed 50–100 mg every 4–6 h as needed. Typically, no more than 300–400 mg a day should
be used.

**Tapentadol**\textsuperscript{236,248}

Tapentadol is a controlled substance CII opioid with an indication for neuropathic pain
associated with DPN. It has a binary mechanism of action centrally acting analgesic that provides
supraspinal μ opioid analgesia to block incoming ascending pathway transmission causing
decremental release of pronociceptive transmitters and spinal analgesia by feedback inhibition
from the brain on the descending noradrenergic (NE) pathway via NE reuptake inhibition (NRI)
for β2 adrenergic receptors pathway and 5-HT reuptake inhibitor. Theoretically, serotonin
syndrome may occur with this agent and with agents that have events upon 5-HT or 5-HT
metabolism. A small, nontherapeutic amount of 5-HT reuptake activity is present in tapentadol
(some subjects in initial clinical trial were using SSRIs and SNRIs without report of a 5-HT
syndrome).

The following are pharmacodynamic drug interactions: alcohol (ethanol), centrally acting
agents [opioids and anesthetics (general)], phenothiazine, antiemetics, tranquilizers, sedatives,
hypnotics [including sodium oxybate (GHB)], and other central nervous system depressants
(consider reduced dose of both agents, doses, and close clinical monitoring). MAOI cautions
prevail. Metabolism at 85% by phase II glucuronidation, conjugation, and 15% phase I as 13% by
2C9 and 2C19 and 2% by CYP450-2D6. Overall, 70% is renal excreted as inactive metabolites and
3% as parent compound.

Consider using one-half of 50-mg dose in patients who require a lower dose based on age, renal,
hepatic function, or complicating comorbidities. Tapentadol has a paucity of euphoria, and no
histamine release has been observed in our patients. Postmarketing events reports include hallucinations, headaches, suicidal reaction, anaphylaxis, angioedema, diarrhea, and palpitations.

**Antiarrhythmics**\(^{235,236,237}\) (Table 9)

Antiarrhythmics block ectopic neuronal activity at central and peripheral sites.\(^ {325}\) Lidocaine, mexiletine, and phenytoin—type I antiarrhythmics—stabilize neural membranes by sodium channel blockade. Lidocaine suppresses spontaneous impulse generation on injured nerve segments, dorsal root ganglia, and dorsal horn wide dynamic range neurons.\(^ {326,327}\) Lidocaine infusions have been used to predict the response of a given neuropathic pain disorder to antiarrhythmic therapy.\(^ {328}\) Lidocaine may be effective at subanesthetic doses, and following nerve blocks analgesia may outlast conduction block for days or weeks.\(^ {328-330}\) It has been reported that patients with PNS injury experience better pain relief than those with central pain syndromes.\(^ {331}\) If a trial infusion of lidocaine is effective, a trial of oral mexiletine is worth considering.

Prior to starting mexiletine, a baseline electrocardiogram is recommended to determine if the patient has underlying ischemic heart disease. Dosages may be increased from 150 to 250 mg three times a day over several days. Taking the medication with food may minimize gastric side effects, which are common and a major reason for discontinuing the drug. Other side effects of mexiletine are nervous system effects, such as tremor and diplopia. Once on a stable dose, a serum level should be obtained (the therapeutic range is between 0.5 and 2.0 mg/ml).

**Topical preparations of local anesthetics**\(^ {237-239}\) (Table 9)

Topical preparations of local anesthetics may be effective for neuropathic pain when there is localized allodynia or hypersensitivity. Topical blockade of small- and large-fiber nerve endings should reduce mechanical and thermal alldynia. A topical lidocaine patch (Lidoderm; 5% lidocaine) has become available, which can be applied to painful areas in shingles (herpes zoster) and in more chronic forms of neuropathic pain, such as diabetic neuropathy or the ischemic neuropathies created by prolonged peripheral vascular insufficiency. Up to three patches may be applied at one time to the painful area. The patches can be worn for up to 12 h a day for PHN and herpes zoster. However, the treating physician must ensure that the patient understands that chronic forms of neuropathic pain may require a longer therapeutic trial, e.g., 30 days, before optimal symptomatic control can be determined. In patients with diabetic neuropathy, Galer et al.\(^ {341}\) have found that the addition of topical lidocaine patches to exogenous GABAergic oral agents may provide further improvement of symptom control.

A topical cream, eutectic mixture of local anesthetic (EMLA cream), a mixture of lidocaine and prilocaine, may also be useful for cutaneous pain. The cream may be applied three or four times a day to the painful area.

**Corticosteroids**\(^ {237-239}\) (Table 9)

Corticosteroids are clearly useful for neuropathic pain, particularly in stimulus-evoked pain such as lumbar radiculopathy. The anti-inflammatory effects of corticosteroids are well known, which may partly explain their efficacy for pain. When administered epidurally for treatment of discogenic radiculopathy, corticosteroids inhibit phospholipase A2 activity and suppress the perineural inflammatory response caused by leakage of disk material around the painful nerve root.\(^ {332}\) However, corticosteroids also act as membrane stabilizers by suppressing ectopic neural discharges.\(^ {240,241}\) Therefore, some of the pain-relieving action of corticosteroids may be due to a lidocaine-like effect.

Depot forms of corticosteroids injected around injured nerves provide pain relief and reduce pain associated with entrapment syndromes. Corticosteroids are also effective if given orally or systemically. In cancer pain syndromes, steroids, such as dexamethasone, may be frontline
therapy for neuropathic pain. The potential side effects of corticosteroids involving multiple organ systems are well known and may be seen by all routes of administration whether given orally, topically, systemically, or epidurally and may include AEs of the skin, soft tissue, ophthalmic, endocrine, cardiovascular, lipid, renal, metabolic, gastrointestinal, musculoskeletal, CNS, immune response, and HPA axis suppression.

**Baclofen**\(^{237–239,333}\) (Table 9)

Baclofen is useful for trigeminal neuralgia and other types of neuropathic pain,\(^{334}\) particularly as an add-on drug. Baclofen is a GABA-B agonist and is presumed to hyperpolarize inhibitory neurons in the spinal cord,\(^{245}\) thereby reducing pain. This GABA effect appears to be similar to benzodiazepines, such as clonazepam. Dose-related side effects of baclofen can be significant and include sedation, confusion, nausea, vomiting, and weakness, especially in the elderly. A typical starting dose is 5 mg three times a day. Thereafter, the drug can be increased slowly to 20 mg four times a day. Abrupt cessation may precipitate withdrawal with hallucinations, anxiety, and tachycardia. The drug is excreted by the kidneys and the dosage must be reduced in renal insufficiency.

**Capsaicin**\(^{237–239}\) (Table 9)

Capsaicin is a C-fiber-specific neurotoxin and is one of the components of hot peppers that produces a burning sensation on contact with mucous membranes. Topical preparations are available over the counter and are widely used for chronic pain syndromes. A capsaicin patch administered under medical supervision is also available. Capsaicin is a vanilloid receptor agonist and activates ion channels on C fibers that are thermotransducers of noxious heat (\(>43^\circ\)C).\(^{335}\) With repeated application in sufficient quantities, capsaicin can inactivate primary afferent nociceptors. For patients with pain due to sensitized nociceptors, capsaicin may be effective, if they can tolerate the pain induced by the medication. The drug causes intense burning, which may abate with repeated applications and gradual inactivation of the nociceptors. However, in patients with tactile allodynia, which is probably mediated by large fibers, capsaicin may not be as effective. Capsaicin extracts are available commercially as topical preparations, containing 0.025% and 0.075% and should be applied to the painful area 3–5 times a day. The preparation may be better tolerated if it is used after application of a topical local anesthetic cream.

**Protein kinase C inhibitors**

Activation of protein kinase C (PKC) has been implicated in noted changes in pain perception. When activated by phorbol esters, PKC enhances thermal hyperalgesia in diabetic mice. Activated PKC also leads to enhancement of EAAs in dorsal horn neurons as well as trigeminal neurons. It is therefore possible that PKC may induce neuronal sensitization that produces hyperalgesia in diabetic neuropathy. Ruboxistaurin, a PKC inhibitor, may be a valid treatment for diabetic neuropathic pain.\(^{336–338}\)

**Transcranial magnetic stimulation**

A recent study found that repetitive transcranial magnetic stimulation (rTMS) was effective for neuropathic pain, particularly for central poststroke pain and trigeminal neuralgia. The effective rTMS for the treatment of neuropathic pain consisted of a train of 200 pulses/min at 20 Hz for 10 min over the identified motor cortex contralateral to the affected side of the body.\(^{148}\) Motor cortex stimulation has also been noted to induce an increase in cerebral blood flow in the ipsilateral thalamus, orbitofrontal, and cingulate gyri as well as in the upper brain stem.\(^{339}\)
Summary and recommendations

Neuropathic pain is a common cause of chronic pain and tends to be resistant to usual doses of traditional analgesic medications. Three classic examples of neuropathic pain include trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy. Neuropathic pain is often described as lancinating or burning in nature. Both types of pain may be present at the same time, often accompanied by allodynia.

Neuropathic pain may be manageable with one monotherapy or more adjuvant analgesic drugs (polypharmacy), often prescribed as part of a comprehensive treatment plan. From a theoretical point of view, it may be helpful to categorize adjuvant analgesics into two broad classes of drugs, agents that act as membrane-stabilizing agents and drugs that enhance dorsal horn inhibition. Membrane-stabilizing drugs may act by blocking sodium and calcium channels on damaged neural membranes. Medications that enhance dorsal horn inhibition appear to act by augmenting spinal biogenic amine and GABAergic mechanisms. From a clinical standpoint, given the paucity of our understanding of neuropathic pain mechanisms and how the medications actually work, it is probably more useful to classify adjuvant drugs according to their traditional therapeutic indications (e.g., antidepressants and anticonvulsants). This point of view is strengthened by the fact that most drugs appear to have multiple mechanisms and sites of action, making further subclassification arbitrary and probably inaccurate.

Anticonvulsants, particularly carbamazepine, gabapentin, and pregabalin are useful for neuropathic pain. Although conventional wisdom suggests that anticonvulsants may be most effective for lancinating pain, anticonvulsants are also useful for burning dysesthesias. The mechanism of action of gabapentinoids (gabapentin and pregabalin) is poorly understood, but these drugs have been demonstrated to bind to the α2delta subunits of the voltage-dependent calcium channel receptors.194 The gabapentinoids reduce the pain due to diabetic peripheral neuropathy and postherpetic neuralgia; gabapentin is an attractive alternative to carbamazepine and tricyclic antidepressants, particularly for patient-specific dosing in elderly patients.

Clonazepam, a benzodiazepine, is another option and also poses at low doses minimal risk from the standpoint of organ toxicity. Clonazepam may be useful for radicular pain and pain associated with tumors, such as plexopathy. In addition, clonazepam may be used to supplement other adjuvant drugs. When given at bedtime, the mild sedating effect of clonazepam can be helpful for patients who have difficulty sleeping because of pain.

Antidepressants (TCAs and SNRIs) have been used effectively for years in the management of multiple pain syndromes, including diabetic neuropathy, postherpetic neuralgia, rheumatoid arthritis, osteoarthritis, migraine headache, low back pain, and fibromyalgia. Pain relief is achieved and accompanied by drug-specific side effects. Studies indicate that only one-third of patients obtain more than 50% pain reduction. Some patients obtain recognized and reported pain relief.

The choice of which antidepressant to use for neuropathic pain often depends on the particular side effect profile of a given drug, because comparisons of individual tricyclic antidepressants and SNRIs have been done to show great differences in efficacy and effectiveness. When a patient is having difficulty sleeping because of pain, a tertiary amine TCA, a more sedating drug, such as amitriptyline may be appropriate. On the other hand, a secondary amine TCA, desipramine, which is considerably less sedating and has fewer anticholinergic effects, may be much better tolerated in elderly patients.

Serotonin-selective reuptake inhibitors (SSRIs) for neuropathic pain have been disappointing, although paroxetine, at relatively high doses, is useful for diabetic neuropathy. Fluoxetine may be useful in the treatment of rheumatic pain conditions, many of which have neuropathic components. As with the tricyclic agents, the SSRIs are probably interchangeable. However, SSRIs are better tolerated than tricyclics and may be extremely effective in treating patients with chronic pain and concomitant depression.

Duloxetine has been approved and granted FDA indications for DPN and milnacipran for fibromyalgia. It remains clear that anticonvulsants and/or antidepressants may be firstline therapy for neuropathic pain. Similar results have been obtained with both, and current
evidence concerning drug efficacy does not support the use of one drug over another. In many cases, selection of a particular drug may depend more on expected side effects (e.g., sedation), patient acceptance/acquisition, and the prescribing clinician’s experience with the drug, than theoretical considerations about mechanisms of drug action. It must be remembered that treatment of neuropathic pain remains largely empirical. In addition, for maximum analgesic benefit, polypharmacy may be necessary. More effective medications may become available, polypharmacy will remain the rule instead of the exception. This is probably understandable, given the multiple mechanisms involved in the pathophysiology of neuropathic pain.

In general, for neuropathic pain either a gabapentinoid and/or an SNRI (duloxetine) should be first-line therapy choices. When considering issues such as time to effective analgesic action and toxicity, gabapentinoids and duloxetine are more attractive and often are our first choice, followed by a tricyclic antidepressant, such as nortriptyline. Both drugs must be started slowly and titrated to therapeutic effect, for full benefit. Tricyclics have many potential nontherapeutic side effects that must be considered, particularly anticholinergic and cardiac interactions and organ toxicity. Occasionally gabapentinoid patients complain of weight gain and non-pitting peripheral edema. Keep in mind that the dosage of gabapentin must be reduced appropriately for patients with renal insufficiency.

An evidence-based treatment algorithm for neuropathic pain treatment was obtained from RCTs using MEDLINE and EMBASE. The tricyclic antidepressants, the SNRI, duloxetine, and the anticonvulsants, gabapentin and pregabalin, were found to be the most frequently studied. In the treatment of neuropathic pain, the lowest number needed to treat (NNT) was for the TCAs, followed by the opioids, and then the anticonvulsants, gabapentinoids and duloxetine. It was felt that the NNT along with the number needed to harm (NNH) were the best way to assess relative efficacy between trials, but they have significant limitations.

When an appropriate medication trial has been ineffective, and all other appropriate medications have been tried and failed or delivered minimal effectiveness, an interdisciplinary pain medicine approach should be considered. Reducing dependence on opioid medications may or may not be a primary goal, depending on whether the pain syndrome is opioid responsive, the patient is demonstrating appropriate improvements in function, and there are not undue side effects or evidence of drug abuse.

Current evidence indicates that nonpharmacological approaches may be reasonable, obviate or reduce the need for potentially toxic medications, and improve the effectiveness of analgesic regimens. Spinal cord stimulation may reduce pain in selected patients. Less invasive techniques, including TENS units and percutaneous nerve stimulation, are also beneficial.

Discussion

The goals of providing medical care for patients with neuropathic pain are often directed by changes in the quality, intensity, timing, and regional distribution of the patients’ symptoms, rather than objective signs or test results of the underlying etiology.

When considering those limitations, it is helpful to target specific symptoms, e.g., burning pain with tricyclic antidepressants and sharp, shooting pain with anticonvulsants. However, from a practical standpoint, pharmacological choices are often based on clinician experience and comfort with the safety and effectiveness/efficacy profiles of a given drug. Until more effective drugs become available, the pharmacological approach remains largely one of patient-specific trial and error. In the meantime, nonpharmacological strategies may assume a larger role in clinical practice. The authors agree that effective management of neuropathic pain requires patience and persistence on the part of both the clinician and the patient. The ability of some patients to accept incomplete pain relief during many therapeutic trials, simply with the hope that an optimal treatment may be determined, provides an example of courage that should be emulated by all health care providers. When a patient’s internal strengths flag due to protracted suffering, physicians should be prepared to treat, or arrange consultative treatment for, the manifest anxiety and depression that often accompany prolonged pain illness.
References


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