ABSTRACT

PURPOSE: To review the use of pharmacotherapy for the treatment of neuropathic pain, with a special emphasis on anticonvulsant medications.

EPIDEMIOLOGY: By conservative estimates, between 0.6% and 1.5% of the US population suffers from conditions leading to neuropathic pain. Most commonly, nearly 6 million individuals seek treatment for pain related to diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN), although the list of underlying etiologies for this type of pain includes a myriad of conditions ranging from infectious diseases to musculoskeletal causes.

REVIEW SUMMARY: The pathophysiology of neuropathic pain and select mechanisms of action and pharmacologic targets for analgesia are discussed. At present, a complete understanding of the precise pathophysiology for this type of pain and the mechanisms of actions for many of these therapeutic agents is lacking; however, several research-based theories are presented. US Food and Drug Administration (FDA)-approved, first-line and second-line medication regimens, including several classes of medications, are reviewed, focusing on anticonvulsant medications and new related agents, such as pregabalin. Specifically, recommendations issued by the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain are discussed. Recommendations are based on the results of multiple, randomized clinical trials, published studies, and the clinical experience of the conference faculty. The 2 types of neuropathic pain emphasized in this article are PHN and DPN. Our understanding of pain mechanisms relate primarily to animal nerve injury models, and confounding psychosocial factors often seen in other less-defined clinical problems as complex regional pain syndrome or low-back pain.

TYPE OF AVAILABLE EVIDENCE: In all examples of recommendations below, randomized, placebo-controlled trials are used. Much of the information comes from the Annals of Neurology 2003, which is the result of an international expert panel using all available evidence for their conclusions on neuropathic pain. All trial data are cited whenever recommendations are made.

GRADE OF AVAILABLE EVIDENCE: Fair

CONCLUSION: A variety of pharmacologic agents from classes including anticonvulsants, antidepressants, and opioids, among others, are available for the management of neuropathic pain—a condition for which our understanding is still in its infancy despite the fact that it afflicts millions of individuals who suffer from diabetes and other chronic illnesses. Decisions regarding which medication to use for management of neuropathic pain may come down to a number of practical considerations. These may include which drugs have US FDA approval; evidence of efficacy and safety from randomized, controlled trials; cost or formulary limitations; and personal experience. In the end, rational polypharmacy—using combinations of multiple medications with different mechanisms of action—may be the most effective means of gaining relief for particularly challenging patients. In the future, research may focus on developing a more complete understanding of neuropathic pain, with the goal of targeting therapies to modulate pain at its source within the nervous system.

(Adv Stud Med. 2006;6(9):399-408)
Although the exact statistics are not known, millions of individuals suffer from neuropathic pain originating from lesions of the central and peripheral nervous systems. While dozens of etiologies of neuropathic pain exist, stemming from conditions ranging from AIDS to alcoholism, 2 of the most common etiologies are diabetes mellitus and herpes zoster. Diabetes mellitus afflicts more than 20 million persons in the United States and an estimated 20% to 24% of these persons experience diabetic peripheral neuropathy (DPN).\(^1\)\(^2\) Herpes zoster strikes an estimated 800,000 persons each year in the United States—most of whom are elderly or immunosuppressed. Using pain at 3 months after rash onset as a definition of postherpetic neuralgia (PHN),\(^2\)\(^3\) between 25% and 50% of adults older than 50 years develop PHN.\(^2\)\(^3\) Overall, conservative estimates of the prevalence of neuropathic pain range from 0.6% to 1.5% of the US population.\(^4\) Work and social activities may be negatively affected, sometimes leading to psychological comorbidities, including anxiety, depression, and sleep deprivation. Diagnosing and treating neuropathic pain are extremely important because proper management will lead to an improvement in quality of life for patients suffering from pain.

**DIAGNOSING NEUROPATHIC PAIN SYNDROMES**

When diagnostic tests reveal a metabolic abnormality (eg, diabetes) or a lesion of the nervous system (eg, multiple sclerosis) compatible with particular symptoms and signs, this provides strong evidence for calling the patient’s pain neuropathic. However, this is not always possible with our current state of diagnostic technology. As a result, the diagnosis of neuropathic pain must most often be based on a history, physical examination, and appropriate laboratory studies, including blood tests, magnetic resonance imaging (MRI), electrophysiologic studies, and, in some cases, nerve or skin biopsy to directly visualize nerve tissue.\(^5\) Making a precise and accurate diagnosis is necessary to guide therapy, as is an understanding of both the underlying pathophysiologic mechanisms of various painful conditions and the mechanisms of actions of the various medications used in treatment.\(^6\)

Neuropathic pain can be constant, intermittent, or both (eg, burning, lancinating, shooting, or electric-shock like). In addition, there may be paresthesias and dyesthesias that may be described as crawling, numbness, itching, or tingling sensations. Patients with neuropathic pain may experience both negative symptoms (numbness) and positive symptoms (burning) and it may be provoked by normal, everyday activities, such as the touch of a bed sheet, the light pressure of clothing, or exposure to environmental elements, such as wind, cold, or heat.

Findings from physical examination may be contradictory and confusing in neuropathic pain. For example, a patient may have diminished sensation and hyperalgesia to pinprick along the same dermatome. A diminished light touch (nonpainful) or pinprick (painful) sensation are both known as hypesthesia; allodynia is also pain in response to normally nonpainful stimuli.\(^7\) Comparing the abnormal side to the normal side of the body may be helpful. In addition to sensory symptoms, patients may also demonstrate motor and autonomic signs, including weakness, muscle stiffness, abnormal sweating, and vascular changes. There is no single diagnostic test for neuropathic pain; MRI, nerve conduction tests, and electromyography can sometimes be helpful in diagnosing specific etiologies, such as radiculopathy stemming from spinal pathology or neuropathy from median nerve compression.

As has already been emphasized, diagnosing neuropathic pain can be a challenge due to its broad base of potential causes, its frequently nonspecific signs and symptoms, and the possibility of psychiatric comorbidities, but it is vital for clinicians to meet the challenge in order to provide appropriate interventions. In the sections later in this article, pharmacologic therapies based upon current understanding of the pathophysiology of pain will be discussed. It is important to note that therapeutic interventions that are effective to treat nociceptive pain are not necessarily effective in the treatment of neuropathic pain.

**UNDERSTANDING THE PATHOPHYSIOLOGY OF PAIN**

To understand the treatment of neuropathic pain, first it is essential to briefly review the various types of pain generated by the body. Nociceptive pain is pain resulting from activity in neural pathways caused by potentially tissue-damaging stimuli.\(^4\) Examples include postoperative pain, arthritis, mechanical low-back pain, sickle cell crisis, and sports or exercise injuries. By contrast, neuropathic pain is pain caused by a primary lesion or dysfunction in the peripheral and/or central nervous systems.\(^7\) For example, peripheral neuropathic pain syndromes include human immunodeficiency virus (HIV) sensory neuropathy, PHN, and DPN. Examples of central neuropathic pain syndromes include central poststroke pain, spinal cord injury pain, and multiple sclerosis pain.

Figure 1 illustrates the ascending pathway of pain transmission during which messages are transduced by the peripheral ending of the primary afferent nociceptor, transmitted to the spinal cord, and relayed via the thalamus to the frontal cortex and somatosensory cortex. Also illustrated is the descending pathway of pain modulation. Changing the transmission of the neurochemical signal traveling along nerves can occur in the periphery, the first synaptic connection at the dorsal
Pain fibres terminate mainly in the superficial dorsal horn (laminae I–II). Ad fibres enter lamina I (and V) and synapse on a second set of neurons. These neurons will carry the signal to the thalamus and are part of the spinothalamic tract (STT). The C fibres enter the spinal cord and synapse on lamina I cells and lamina II interneurons—neurons that make synaptic connections with other cells within the local environment. The interneurons convey the signal to the STT cells that reside mainly in laminae I, IV, and V. The axons of the STT cells project across the spinal cord to the STT, which is located in the ventrolateral quadrant of the contralateral spinal cord white matter.

The STT transmits information about temperature and pain, as well as “simple” touch (ie, related to localization of stimulus) and visceral sensations. It mediates the discriminative and arousal-emotional components of these sensations by separating out the “fast” (discriminative aspect) and “slow” (affective aspect) components of pain into different regions of the tract that are transmitted in parallel to the thalamus. Discriminative pain reaches the thalamus directly without making connections elsewhere in the nervous system, whereas arousal-emotional pain reaches the thalamus indirectly via connections with brainstem regions. Slow pain is also transmitted by other pathways such as the spinoreticular tract.

The STT may be divided into the lateral STT and the anterior STT. Pain and temperature is transmitted mainly in the lateral STT. The lateral STT conveys sensations of both fast and slow pain. The anterior STT conveys sensations of simple touch (stimulus localization). The STT ascends the entire length of the cord and the brainstem, staying in about the same location all the way up. It is here in the brainstem that the different modalities separate out to terminate in different thalamic and brainstem nuclei. The fast pain STT axons terminate in the ventroposterior nucleus, which comprises the ventral posterolateral (VPL) and ventral posteromedial (VPM) and the posterior (PO) nuclei. These axons seem to mediate mainly the sense of “simple touch” and pain. These sensations are separated within the thalamus: neurons in the VPL and VPM do not respond specifically to noxious stimulation, whereas cells in the PO receive inputs from both low- and high-threshold afferents. These cells are associated with the conscious perception of pain.

The slow pain-STT axons innervate the nonspecific intralaminar nuclei of the thalamus, and the reticular formation in the brainstem. These axons form at least part of the forebrain pain pathway associated with the affective quality (unpleasantness and fear of further injury) of pain and can be dissociated from the discriminative quality (the type and nature of the injury itself). The projections to the reticular formation may underlie the arousal effects of painful stimuli. The arousal itself may activate noradrenergic neurons in the locus coeruleus, and thus decrease the upward pain transmission. This may be an example of a negative feedback loop in the nervous system.

produced that result in a hyperexcitable nerve. In damaged nerves, abnormal sodium channels may be abnormal, nerve impulses that may promote pain peripherally.10,11 Alternately, damaged nerves may produce ectopic, or spontaneous, discharges. A rarer mechanism of neuropathic pain may occur with deafferentation—if the CNS is deprived of normal nerve input, as in the case of amputation or plexus avulsion, pain may result. The classic picture is severe pain in an insensate (or absent) limb.

According to the excitotoxicity theory, nerve damage results in a barrage of nociceptive input released into the spinal cord that can damage inhibitory cells and result in a disinhibited pain system. Another theory holds that, in damaged nerves, abnormal sodium channels may be produced that result in a hyperexcitable nerve. Alternatively, damaged nerves may produce ectopic, or abnormal, nerve impulses that may promote pain perceptions. These discharges are termed “ectopic” because they do not originate from nociceptors. Spontaneous discharges can originate in peripheral or central neurons and may be mediated by abnormal expression of sodium channels in injured peripheral nerves from local patches of demyelination, and somata in dorsal root ganglia.

Peripheral nociceptors may become sensitized by nerve injury or by repeated stimulation. Sensitization results in a lower threshold for pain transmission mediated by upregulation of specific neuronal membrane proteins. Inflammatory signaling molecules cause protein kinases in the peripheral neurons to phosphorylate sodium channels, changing their properties to lower their activation threshold, and to generate a larger current when activated. Gene transcription may also be altered at dorsal root ganglia and dorsal horn neurons—all of which may result in increased heat sensitivity and a lower firing threshold.

Finally, with central sensitization, there is repeated sensory input from injury or persistent stimulation, and the CNS may become hyper-responsive (sensitized) to peripheral input, a so-called facilitated state. This state is caused by long-term or permanent changes in the anatomy or physiology of the CNS produced by pain.13 CNS neurons then increase their spontaneous activity and respond more robustly to incoming signals. Central sensitization can contribute to spreading hyperalgesia, referred pain, allodynia, and persistent spontaneous pain.17 These changes are the result of biochemical and/or cellular changes in central pain pathways. Specifically, there may be modification of gamma aminobutyric acid (GABA) and glycine receptors resulting in a reduction of inhibition of pain transmission and/or activation of N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptors leading to a lowering of the firing threshold. Long-lasting changes may result from altered receptor expression and inhibitory interneuron death.

SELECT MECHANISMS OF ACTION AND PHARMACOLOGIC TARGETS FOR ANALGESIA

Depending on the specific drug, agents used for management of neuropathic pain may control peripheral and/or central pain via several mechanisms, including interference with sodium channels, inhibition of excitatory transmission as mediated by glutamate and NMDA receptors, and/or increased inhibition of GABA-mediated signals. Because intracellular calcium is required for neurotransmitter release and signal propagation, one way to attenuate inappropriate pain signals is to limit calcium entry into hyperexcitable neurons. Voltage-gated calcium channels allow the selective permeability of calcium ions across presynaptic plasma membranes in response to a presynaptic action potential. Pregabalin, a new anticonvulsant related to gabapentin and structurally similar to GABA, works by binding to the voltage-gated calcium channels adjacent to neuronal synaptic vesicles. In contrast to calcium channel blockers, such as verapamil used in the treatment of hypertension or heart disease, pregabalin does not block or reduce current from L-type calcium channels and is not associated with a reduction in blood pressure or changes in heart rate. Furthermore, although the pregabalin binding protein is also found in association with calcium channels of other tissues, such as skeletal muscle, binding in such non-neuronal tissues is not thought to result in any pharmacological activity. Pregabalin and gabapentin are the only marketed drugs that are known to bind to the alpha2-delta subunit. Other analgesics, anticonvulsants, anxiolytics, and a variety of other CNS-active compounds do not bind at this site.

Animal studies conducted by Fehrenbacher et al demonstrated another potential mechanism of action for gabapentin and pregabalin; specifically, decreased release of the excitatory neurotransmitter, substance P, under conditions when neurons are hyperexcited by either prior inflammation or activation of cellular protein kinase signals.

Other anticonvulsant medications, including carbamazepine and lamotrigine, have also demonstrated evidence of efficacy in DPN and PHN in a number of clinical trials, but unlike gabapentin and pregabalin,
these have different mechanisms of action.\textsuperscript{23–27} In the case of carbamazepine, there is a blockade of the sodium channels, with decreased influx of calcium and an influence on NMDA receptors. Likewise, lamotrigine has an inhibitory effect on voltage-sensitive sodium channels, stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (eg, glutamate and aspartate).

It is important to emphasize that a complete understanding of how various drugs may mitigate pain is still in its infancy. Furthermore, in an individual patient, more than one pathophysiologic mechanism probably is relevant. The ability to classify patients based on predominant pathophysiology may, hopefully, help target the therapy.

In addition, at various points along the pain pathway (Figure 1), various medications may have their respective mechanisms of action. For example, medications such as venlafaxine and duloxetine may intervene in the descending modulatory pathways through enhanced norepinephrine/serotonin levels in the CNS. Opioids have a variety of effects in the central and peripheral nervous system but have their primary analgesic action on the dorsal horn. Rational polypharmacy employs more than one drug, working in tandem employing different mechanisms of action to achieve a common goal of pain management.

**TREATMENT OF NEUROPATHIC PAIN**

The Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain has issued recommendations for first-line pharmacologic treatment of neuropathic pain.\textsuperscript{7} Recommendations are based on the results of multiple, randomized clinical trials, published studies, and the clinical experience of the conference faculty. The 2 types of neuropathic pain emphasized in this article are PHN and DPN because it is for these types of pain that the great majority of randomized controlled trials of treatments for neuropathic pain have been conducted, and because our understanding of the mechanisms of neuropathic pain is due largely to those studies.

Agents have been available for the treatment of neuropathic pain since the 1960s (Figure 2). The above consensus guidelines were published in 2003; since then, 2 new drugs have received US Food and Drug Administration (FDA) approval for neuropathic pain: duloxetine and pregabalin. Duloxetine became the first drug approved for DPN and pregabalin was the first drug approved for both neuropathic pain conditions PHN and DPN. Together, these medications comprise first-line therapies for the treatment of neuropathic pain. Other first-line medications include opioid analgesics, tramadol, and tricyclic antidepressants (TCAs; eg, amitriptyline, nortriptyline, and desipramine). Each of these first-line agents will be examined as individual medications or by classes of drugs.

**ANTICONVULSANTS**

Three drugs in this category have US FDA approval and others have at least 1 randomized controlled trial showing efficacy. Many of the anticonvulsants have differing mechanisms of action, including sodium channel blockers (topiramate, zonisamide, oxcarbazepine, carbamazepine, gabapentin, and pregabalin), decreasing NMDA activity (topiramate, lamotrigine, valproate, and carbamazepine), N-type calcium channel modulators (lamotrigine and oxcarbazepine), T-type calcium channel modulators (valproate), L-type calcium channel modulators (gabapentin and pregabalin), increasing gamma amino butyric acid (lamotrigine, tiagabine, and valproate), and other mechanisms. The variety present in the anticonvulsants leads to the possibility of combining agents in this category when pain control is suboptimal. Listed later in this section are the anticonvulsants with US FDA approval listed in order of acceptance by the US FDA.

**Carbamazepine.** Carbamazepine, although an antiepileptic drug (AED), bears a structural similarity to TCAs. It has a well-established beneficial effect in trigeminal neuralgia, and is approved by the US FDA. Carbamazepine blocks sodium channels, decreases influx of calcium in sensitized dorsal root nociceptors, and has an effect on the NMDA receptor. Similar to many AEDs, carbamazepine may cause drowsiness, dizziness, and more seriously leukopenia and hepatotoxicity. Rarely, carbamazepine has been implicated in agranulocytosis, aplastic anemia, and inappropriate
antidiuretic hormone levels. Multiple drug interactions occur with this AED.

Monitoring of the blood count and liver function tests are recommended, especially after first initiating treatment with carbamazepine. Patients generally may be started at doses between 100 and 200 mg daily, and then titrated to a maximum of 1200 mg daily. Serum carbamazepine levels may help determine the appropriate dose.

**Gabapentin.** Gabapentin is one of the second-generation AEDs whose chemical structure is related to the inhibitory neurotransmitter, GABA. Eight double-blind, placebo-controlled, randomized clinical trials of gabapentin for chronic pain found that, at daily dosages up to 3600 mg, gabapentin significantly reduced pain compared to placebo in patients with PHN, DPN, and mixed neuropathic pain syndromes, among other neuropathic disorders. On the basis of 2 large randomized trials, the US FDA approved gabapentin for treatment of PHN. The first was a multicenter, randomized, double-blind, placebo-controlled, parallel design, 8-week trial involving 229 subjects (113 patients received gabapentin, and 89 [78.8%] completed the study; 116 received placebo, and 95 [81.9%] completed the study). Subjects receiving gabapentin had a statistically significant reduction in average daily pain score from 6.3 to 4.2 points compared to a change from 6.5 to 6.0 points in subjects randomized to receive placebo ($P < .001$). There were also statistically significant improvements in secondary pain parameters and sleep ($P < .001$). The authors concluded that gabapentin is effective in the treatment of PHN pain and sleep interference and that mood and quality of life also improve with gabapentin therapy.

The second study was also a multicenter, double-blind, randomized, placebo-controlled 7-week study to evaluate the efficacy and safety of gabapentin in dosages of 1800 or 2400 mg/day for treating PHN in 344 subjects. From week 1, pain scores showed a significantly greater improvement with gabapentin: the final difference from baseline was -34.5% for the 1800-mg dose compared to -15.7% for the placebo group. The difference versus placebo was 18.8% for the 1800-mg dose (95% confidence interval, 10.9%–26.8%; $P < .01$) and 18.7% for the 2400-mg dose (10.7%–26.7%; $P < .01$). In addition, sleep improved significantly and in a similar manner.

Gaba
pentin therapy should begin at low dosages and then be titrated gradually to maximize patient adherence and minimize side effects: 100 to 300 mg in a single dose at bedtime or 100 to 300 mg 3 times daily. Titration then occurs every 1 to 7 days by 100 to 300 mg as tolerated. Target dosages that demonstrated benefits for neuropathic pain ranged from 1800 mg per day (the US FDA-approved dosage for PHN) to 3600 mg per day. The final dosage should be determined either by achieving complete pain relief or by the development of unacceptable adverse effects. An adequate trial of gabapentin would include 3 to 8 weeks for titration to allow the development of tolerance to adverse effects, plus 1 to 2 weeks at the maximum tolerated dosage.

The adverse effects of gabapentin include dizziness, somnolence, edema, fatigue, ataxia, nystagmus, short-term memory loss, and weight gain. Because more than 95% of the drug is excreted in the kidney, dosage adjustment is necessary in patients with renal insufficiency. However, it is generally safe, well tolerated, and free of drug interactions.

**Pregabalin.** Pregabalin is an alpha2-delta ligand chemically related to gabapentin, and also indicated for the management of neuropathic pain associated with DPN and PHN. Its mechanisms of action has been previously discussed in this review. The efficacy of pregabalin for DPN was established in 3 double-blind placebo-controlled, multicenter studies that involved 729 patients with type 1 and type 2 diabetes mellitus. Treatment with pregabalin at dosages of 100 to 200 mg 3 times a day significantly improved mean pain scores and increased the proportion of patients with 50% or higher reduction in pain scores from baseline.

Likewise, pregabalin was studied in 3 trials of patients with PHN. These were double-blind, placebo-controlled, multicenter studies enrolling 799 patients of whom 566 completed the studies. All patients had neuralgia for at least 3 months after rash. Pregabalin at dosages ranging from 75 to 300 mg twice daily compared to placebo reduced pain scale ratings significantly, and also increased the proportion of patients who achieved at least a 50% reduction in their pain scores from baseline compared to placebo. The starting dose of pregabalin is 50 mg 3 times daily, but can be titrated up to 100 mg 3 times a day. Common adverse effects are dizziness and somnolence, followed by ataxia, neuropathy, and peripheral edema, similar to gabapentin.

Pregabalin and gabapentin are US FDA-approved anticonvulsants having received this indication before trials proved an analgesic effect. No head-to-head blinded trials have been done showing that either drug is more efficacious.

**Other Anticonvulsants**

**Lamotrigine.** Lamotrigine has shown efficacy in clinical trials for trigeminal neuralgia, DPN, HIV-related neuropathy, and central poststroke pain. Eisenberg et al compared lamotrigine to placebo in DPN over a 6-week period. Pain scores in the lamotrigine-treated group were reduced from 6.4 ± 0.1 to 4.2 ± 0.1, and in the control group from 6.5 ± 0.1 to 5.3 ± 0.1 ($P < .001$ for lamotrigine doses of 200, 300, and 400 mg), and side effects were equivalent in both groups. Lamotrigine decreases GABA and NMDA, and blocks...
sodium and calcium channels. Similar to other AEDs, dizziness and sleepiness are common adverse reactions; however, the prescribing information for lamotrigine also includes a boxed warning for severe rash associated with Stevens-Johnson syndrome and toxic epidermal necrolysis. Very slow titration lowers this risk considerably but makes lamotrigine a more difficult drug to use.

Other anticonvulsants (eg, levetiracetam, tiagabine, topiramate, and zonisamide) are commonly used to treat neuropathic pain, but lack randomized trial evidence of efficacy.

**Antidepressant Medications**

**Tricyclic antidepressants.** Antidepressant medications have also been used off-label for many years in pain management. Thirteen consecutive well-designed, randomized trials have shown that TCAs, including nortriptyline, desipramine, and amitriptyline, reduce pain in both DPN and PHN. However, comparing amitriptyline to nortriptyline, nortriptyline was found in one study to be superior in terms of adverse effects. Watson et al conducted a randomized, double-blind, crossover trial of amitriptyline versus nortriptyline in 33 patients. Twenty-one of the 31 (67.7%) who completed the study had at least a good response to either or both antidepressants in terms of pain relief; however, intolerable side effects were more common with amitriptyline. Indeed, the primary problem with use of TCAs is side effects; caution is advised in patients with histories of cardiovascular disease, untreated narrow-angle glaucoma, and urinary retention. Screening patients with an electrocardiogram prior to starting a TCA is recommended looking for prolongation of the QT interval. TCAs could increase this abnormality leading to serious arrhythmias. In addition, the American Geriatric Society’s analgesic guidelines warn against the use of amitriptyline in older patients due to side effects. Drugs metabolized by the cytochrome P450 2D6 system, including selective serotonin reuptake inhibitors (SSRIs), duloxetine, and cimetidine, compete with the TCAs resulting in higher drug levels of the TCA. Dosages effective for the treatment of depression are generally higher than that necessary for pain management, typically starting at 10 to 25 mg at bedtime, and then titrated every 3 to 7 days by 10 to 25 mg per day as tolerated to dosages of 75 to 150 mg per day as tolerated. Generally, patients tend to respond to TCAs early in treatment, but need a course of at least 6 weeks before this treatment is considered a failure.

**Duloxetine.** Duloxetine is a serotonin and noradrenergic reuptake inhibitor (SNRI) with a purported mechanism of action involving enhanced descending inhibitory pathways from the locus coeruleus (norepinephrine) and raphe nuclei (serotonin). The precise mechanism has not been worked out in humans. There is strong clinical evidence that both serotonin and noradrenaline are necessary to optimally treat chronic/persistent pain. Multiple studies have shown a lack of efficacy of the pure serotonin reuptake inhibitors in treating multiple pain states, including neuropathic pain.

The efficacy of duloxetine for the management of neuropathic pain associated with DPN was established in 2 randomized, 12-week, double-blind, placebo-controlled, fixed-dose studies. Treatment with duloxetine at 60 mg daily significantly reduced 24-hour average pain levels compared to placebo. In these trials, 58% of 1074 patients treated with duloxetine reported at least a 30% sustained reduction in pain. Duloxetine can cause nausea, somnolence, dizziness, anorexia, and constipation. Nausea is the most troublesome side effect and can be tempered by starting at 20 or 30 mg daily for the first week.

Because duloxetine is an antidepressant, it carries the black-box warning of increasing the risk of suicide in a depressed population. Many chronic pain patients are also depressed, and suicide should be actively screened when initiating treatment. Duloxetine or other antidepressants do not increase suicidality in patients without depression, even if they suffer from persistent pain.

Duloxetine is metabolized in the liver and is a competitive inhibitor of 1A2 and 2D6. The TCAs are also metabolized through 2D6, leading to higher blood levels when duloxetine is used with a tricyclic. Duloxetine increases serotonin levels, thus it should not be used concomitantly with SSRIs.

In a large review of all placebo-controlled clinical trials of painful neuropathy, it was shown that 6.7 patients would need to be treated with SSRIs to achieve 50% pain relief in 1. That number is somewhat better with TCAs (3.4), which are SNRIs, but it falls to 2.0 for dual-action agents and to an almost-optimal 1.4 with dual-action agents, which are titrated to optimal doses.

**Venlafaxine.** Another SNRI, venlafaxine has been studied for the treatment of DPN in 1 randomized trial and another trial compared venlafaxine with imipramine for the treatment of painful neuropathies. Venlafaxine extended release in 2 doses (75 mg/day or 150–225 mg/day) was compared to placebo for the treatment of DPN. To enter the trial, patients had to have pain scores of 4 or higher, 3 months or more of pain, and be without depression. After 3 weeks of titration to appropriate doses, follow-up pain scores showed a significant reduction in pain only in the higher-dose group. At lower doses, venlafaxine works mainly on increasing serotonin by reuptake inhibition, whereas above 125 mg/day, norepinephrine levels also increase causing it to be an SNRI at these doses. Less than 10% of the active treatment group discontinued the study due to side effects, most common of which were nausea, somnolence, dyspepsia, and sweating. At higher doses, blood pressure can
increase and should be monitored. Peripheral edema also occurs and can be bothersome. Only 5% of the male patients reported erectile dysfunction.

**Transdermal 5% Lidocaine**

Transdermal 5% lidocaine, as the name implies, is a topical medication that delivers a local anesthetic to the site of the pain. In 2 double-blind, vehicle-controlled randomized clinical trials, transdermal 5% lidocaine provided statistically significantly greater pain relief to patients with PHN than did vehicle-control patches without lidocaine. Rowbotham et al studied 35 individuals with established PHN who used transdermal 5% lidocaine to cover the area of greatest pain (specifically allodynia) as fully as possible.\(^5\) Lidocaine-containing patches were applied in 2 of 4, 12-hour long sessions; in 1 session, vehicle patches were applied, and 1 session was a no-treatment observation session. Lidocaine-containing patches significantly reduced pain intensity at all time points up to and including 12 hours compared to no-treatment observation and to vehicle patches. There was minimal systemic absorption of lidocaine; therefore, patch application was without systemic side effects and was well tolerated.\(^5^5\)

In a second study also involving patients with PHN, 25 of 32 (78.1%) subjects preferred the transdermal 5% lidocaine treatment phase as compared to 3 of 32 (9.4%) of subjects in the placebo patch phase (\(P < .001\)) of this crossover study. Furthermore, there was no statistical difference between the active and placebo treatments with regard to side effects.\(^5^4\) On the basis of those studies, the US FDA approved lidocaine for treatment of PHN. Because transdermal 5% lidocaine is topical, there is little systemic absorption, it is easy to use, and adverse effects are generally limited to a rare skin irritation. The package insert recommends applying the patch in cycles of 12 hours on and 12 hours off because this is the way the drug was studied. Transdermal 5% lidocaine has been studied with continuous application demonstrating prolonged analgesia and minimal side effects.

**Opioid Analgesics and Tramadol**

Opioids and tramadol are approved for general pain indications and have been studied in neuropathic pain.\(^5^9\) Five double-blind, randomized trials of oral opioid analgesics have been published involving patients with PHN, who experienced significantly greater pain relief and improvements in functionality after therapy with oxycodone compared to placebo. For example, Watson and Babul administered either controlled-release oxycodone 10 mg or placebo every 12 hours, each for 4 weeks, to 50 patients with PHN.\(^5^6\) The dose was increased weekly up to a possible maximum of 30 mg every 12 hours. Pain intensity and pain relief were assessed on a daily basis. The oxycodone dose during the final week was 45 ± 17 mg per day. Compared to placebo, oxycodone resulted in significant pain relief (including steady pain, allodynia, and paroxysmal spontaneous pain).\(^5^6\)

In a second study of patients with DPN, controlled-release oxycodone titrated to 120 mg/d significantly improved pain and sleep, in addition to ability to perform daily activities, compared to placebo.\(^5^7\) This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 159 subjects with moderate to severe pain due to diabetic neuropathy. Treatment began with either 10 mg of controlled-release (CR) oxycodone (\(n = 82\)) or identical placebo (\(n = 77\)) every 12 hours. Doses could be increased every 3 days to a maximum of 6 tablets (60 mg CR oxycodone) every 12 hours. Treatment lasted up to 6 weeks. The primary efficacy variable was overall average daily pain intensity during study days 28 to 42. Controlled-release oxycodone provided more analgesia than placebo (\(P = .002\)), but also caused more adverse effects: overall, 80 of 82 (96%) subjects given CR oxycodone and 52 of 77 (68%) subjects who received placebo reported adverse events, and these were generally typical opioid side effects.

The most common adverse effects of opioid analgesics are constipation, sedation, and nausea. Serious side effects are not common and opioids can be used effectively even in the elderly. Opioid analgesics may be used in patients with a history of substance abuse, but close monitoring is required. Physical dependence is characterized by withdrawal symptoms if the opioid is stopped abruptly. A patient becoming physically tolerant, on the other hand, demonstrates the need for more opioid to have the same analgesic effect. Neither physical dependence nor physical tolerance should be confused with psychological dependence or addiction, which is a behavioral syndrome characterized by craving, compulsive use of the opioid, and continued use despite clear harmful effects of the drug.

Tramadol is a weak norepinephrine and serotonin reuptake inhibitor, and a weak opioid agonist. It is classified as an opioid, but the potential for misuse and addiction with tramadol is uncommon and it is the opioid that does not have Drug Enforcement Agency scheduling. In 2 double-blind, placebo-controlled, randomized clinical trials in patients with DPN and in patients with painful polyneuropathies, tramadol titrated to a maximum dosage of 400 mg per day also was significantly better at relieving pain than placebo.\(^5^8,5^9\)

The adverse effects of tramadol include dizziness, nausea, constipation, somnolence, and orthostatic hypotension. Its use should be avoided in those who have a history of seizure disorder and in those who may be using other serotonergic medications, especially SSRIs and monoamine oxidase inhibitors. Similar to opioid medications, tramadol may cause cognitive impairment in elderly patients.
Tramadol should be titrated from low dosages of 25 mg once or twice daily to a maximum dosage of 100 mg 4 times daily, depending on patient reaction; it may take 4 weeks to determine if the medication is effective for the pain. Tramadol is also available in combination with acetaminophen and a long-acting agent administered once daily. The extended-release preparation should be titrated just like the immediate-release compound, with a maximum daily dose of 300 mg.

CONCLUSIONS

Pain management is changing rapidly and constantly. With the plethora of drugs available for the treatment of neuropathic pain, an evidence-based decision algorithm would be wise. Multiple groups, including the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain, could not agree on specific, restricted treatment recommendations.1 Treatments were put in groups of first-line and second-line agents. The decision then becomes clinical directed by guidelines, but with many other factors to consider as with any clinical decision—cost, clinician experience, safety, and patient comorbidities play as important a role as randomized trials or US FDA approval. The multiple drugs and drug classes available makes the treatment decision very difficult to the clinician not familiar with all the choices. Yet, the great variety of treatment options also gives the informed provider more flexibility than ever before, granting the patient hope that something can be done to control the relentlessness of neuropathic pain. Perhaps, in the near future, researchers will be able to gain a clearer understanding of this still enigmatic phenomenon of neuropathic pain, and thus be able to guide clinicians toward a more precise selection of therapeutic interventions to suit the particular pathophysiologic mechanism that is in play.

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