Painful Peripheral Neuropathy

*Gil I.Wolfe, MD**
Richard J. Barohn, MD

Address
*Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8897, USA.
E-mail: gil.wolfe@utsouthwestern.edu

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Opinion statement

- Treatment of neuropathic pain is the primary focus of management for many patients with painful peripheral neuropathies. Neuropathic pain is a common feature of many peripheral neuropathies including those associated with diabetes, uremia, HIV infection, and alcohol abuse. Pain is also present in the majority of patients with idiopathic sensory and sensorimotor polyneuropathies.
- A growing number of pharmacologic agents are available for the treatment of neuropathic pain. The medications that have undergone the most rigorous study are the tricyclic antidepressants and anticonvulsants. These two families of medications are widely used and represent first-line agents in the management of neuropathic pain [1••].
- Pain management should begin with a concerted effort to identify the etiology of the neuropathy, as directed therapy may help alleviate the symptoms. When initiating pharmacotherapy for neuropathic pain, one must individualize treatment and choose an agent that is likely to be tolerated, as adverse events are not uncommon for some of the medications. Treatment of neuropathic pain remains challenging, with considerable variability in an individual's response to the various agents and even to different drugs in the same class. However, monotherapy with a well-chosen agent or rational polypharmacy that combines medications with different mechanisms of action will benefit a majority of patients with neuropathic pain.

Introduction

Primary care physicians, neurologists, and other specialists commonly encounter peripheral neuropathies associated with neuropathic pain. It has been estimated that neuropathic pain affects at least 2% of the US population. Painful peripheral neuropathies can be challenging to evaluate and treat. The cause of the peripheral neuropathy may remain unknown in a majority of patients [2], the so-called idiopathic or cryptogenic sensory polyneuropathies [3,4]. The inability to identify a specific etiology for the neuropathy can be frustrating for both patients and their clinicians. Of identifiable etiologies, diabetes and alcohol abuse are the most common, but there are a large number of other causes (Table 1).

DEFINITION

The conventional definition of neuropathic pain is pain resulting from injury to or dysfunction of the nervous system in the absence of direct nociceptive input. The injury or dysfunction may involve peripheral or central nervous system structures.

The symptoms of neuropathic pain are generally referred to as the "positive" symptoms of peripheral neuropathy. Paresthesias are abnormal spontaneous or stimulus-independent sensations that may be described as tingling or compared with a body part that is "asleep." Descriptors of spontaneous painful sensation vary widely in these patients and include burning, stabbing, stinging, squeezing, aching, cramping, shooting, and freezing. "Pins and needles, broken glass, and vice-like" sensations may be elicited by history. Stimulus-evoked pain is also common and is experienced in a variety of forms. Dysesthesia refers to discomfort generated by contact with an object, allodynia to pain following contact by a normally innocuous stimulus, and

Table 1. Causes of painful peripheral neuropathy

- Major causes of painful peripheral neuropathy
  - Idiopathic or cryptogenic
  - Diabetes
  - Alcohol abuse and malnutrition
  - HIV infection or AIDS
  - Post-herpetic
- Other causes of painful peripheral neuropathy
  - Amyloidosis
  - Cancer
  - Fabry disease
  - Guillian-Barré syndrome
  - Hereditary sensory and autonomic neuropathies (HSAN)
  - Leprosy
  - Lyme disease
  - Medications
    - Metronidazole
    - Misonidazole
    - Nitrofurantoin
    - Suramin
    - Taxol
    - Thalidomide
    - 2',3'-dideoxycytidine (ddC)
    - 2',3'-dideoxyinosine (ddI)
  - Porphyria
  - Sarcoidosis
  - Sjögren's syndrome
  - Tangier disease
  - Toxins
    - Arsenic
    - Thallium
  - Vasculitis
  - Vitamin deficiency
    - Thamine
    - Pyridoxine (vitamin B6)
    - Pantothenic acid
    - Cobalamin (vitamin B12)
  - Uremia

hyperpathia to exaggerated pain from a noxious stimulus. A variety of positive symptoms often coexist in an individual. Given the length-dependent pattern of many peripheral neuropathies, neuropathic pain symptoms tend to predominate in the distal limbs, typically involving the feet to a greater degree than the hands. As an example, in a cohort of 117 patients presenting with painful, burning feet, 89% had laboratory evidence of a peripheral neuropathy [2].

OVERVIEW OF PAIN MECHANISMS

The pathophysiologic basis of neuropathic pain is complex and not fully understood, but a number of mechanisms have been proposed. Peripheral mechanisms include altered sensitivity and activation of C nociceptor terminals resulting in ectopic discharges in damaged or regenerating fibers, recruitment of silent nociceptors, and spontaneous discharges in more proximal segments of the sensory nerve, including the dorsal root ganglion. Change in sodium channel expression and permeability appears to be a common event in these peripheral alterations, and many pharmacologic agents used in neuropathic pain have activity at these ion channels. Damaged peripheral nerve fibers express a-adrenoreceptors and exhibit heightened sensitivity to sympathetic stimulation, raising the possibility of a sympathetically mediated component to neuropathic pain states [5]. Waves of increased peripheral nerve activity move centrally, producing central sensitization in second- and third-order neurons. Central sensitization appears to result from increased and prolonged release of excitatory amino acids such as glutamate and neuropeptides [6•]. The release of substance P with prolonged activity along nociceptive pathways, for instance, can potentiate activation of post-synaptic *N*-methyl-d-aspartate (NMDA) receptors. Additional ion channels are subsequently opened, enhancing the generation of action potentials in central sensory pathways. In addition, neuropeptides may diffuse through the dorsal horn, sensitizing neurons that would otherwise be "bystanders," producing the phenomenon of enlarged peripheral receptive fields. The perception of pain over a wider distribution with greater intensity and duration results. Of the newer pharmacologic agents found efficacious in neuropathic pain, many are thought to inhibit central sensitization by blocking the activity of glutamate, excitatory neuropeptides, and presynaptic calcium channels, or enhancing inhibitory pathways such as those mediated by gamma-aminobutyric acid (GABA) and its receptors.

In addition, according to the classical "gate control" theory of Melzack and Wall [7], the loss of large-fiber input from an underlying neuropathic injury may disinhibit spinal cord pathways that would normally dampen the transmission of painful stimuli through small-fiber afferents, thereby enhancing the pain experience. The gate control theory provides some basis for the many electrical stimulation techniques that have entered the pain field. A variety of pathophysiologic processes may be at work in an individual patient, and the same mechanisms may not be present in all patients who share a specific neuropathic pain state. This pathophysiologic variability likely accounts for some of the heterogeneity of patient responses to therapeutic interventions [8].

TREATMENT GUIDELINES

Pain management should begin with a concerted effort to identify the etiology of the neuropathy, as directed therapy may help alleviate the symptoms. When initiating pharmacologic or nonpharmacologic therapies, a number of general guidelines should be followed including the following: 1) the patient and physician agree that the goal is

to identify an effective therapy with tolerable side effects; 2) understand that the response can vary considerably between patients and that pain relief is rarely complete; 3) initiate mediations at low doses, titrating them slowly until an adequate clinical response is observed or intolerable side effects appear; and 4) consider polypharmacy or multidimensional therapy approaches when one drug provides partial relief, but higher doses produce troublesome side effects. In this setting, adding a medication or initiating a non-pharmacologic modality that has a different mechanism of action is a rational approach.

An oral drug trial of at least 4 to 6 weeks is recommended before switching to or adding another medication. Shorter trials can be considered with topical agents, although capsaicin cream should be continued for at least 3 to 4 weeks, and patients should be warned that neuropathic pain symptoms might worsen initially with capsaicin.

Table 2. Recommendations for pharmacotherapy of painful peripheral neuropathy

First-line	Route
Tricyclic antidepressants	Orally
Carbamazepine	Orally
Gabapentin	Orally
Capsaicin	Topical
Second-line	**Route**
Tramadol	Orally
Lamotrigine	Orally
Topiramate	Orally
Lidocaine patch	Topical
Third-line	**Route**
Venlafaxine XR	Orally
Mexiletine	Orally
Chronic opiates	Orally

Treatment

Diet and lifestyle

- Avoid excessive alcohol intake. In general, patients with neuropathy should limit consumption to one serving of alcohol daily. If the neuropathy is related to alcohol abuse, abstinence should be stressed.
- Maintain a balanced diet. Patients with diabetes should follow appropriate American Diabetes Association guidelines.
- Encourage the development of coping skills, stress management, relaxation techniques, and biofeedback.
- Multivitamin supplementation can be considered, especially in patients with neuropathy related to alcohol abuse. However, overuse of pyridoxine (more than 200 mg per day) should be avoided.

Pharmacologic treatment

- A number of randomized, double blinded trials have found tricyclic antidepressants—imipramine, amitriptyline, desipramine, and clomipramine—to be superior to placebo in painful diabetic neuropathy [8,9, Class I]. Both carbamazepine and gabapentin, have reduced the pain of diabetic neuropathy in well-designed studies [10•,11, Class I]. Recently, tramadol, a primary analgesic, demonstrated efficacy in diabetic and other forms of painful polyneuropathy [12,13•, Class I]. Capsaicin cream, a chili-derived alkaloid that depletes the neurotransmitter substance P from sensory nerves, also has reduced neuropathic pain in a majority of placebo-controlled studies, although the effectiveness of blinding has been questioned [1••,14, Class I].
- Using a numbers-needed-to-treat methodology based on data from randomized, placebo-controlled, double blinded trials, tricyclic antidepressants were recently recommended as first-line therapy for neuropathic pain [1••]. Gabapentin, carbamazepine, and tramadol were the leading alternatives (Table 2).

Tricyclic antidepressants

	Tricyclic antidepressants have been tested and are used extensively in a variety of neuropathic pain syndromes including diabetic neuropathy and post-herpetic neuralgia [8,9, Class I]. Efficacy for the individual agents (amitriptyline, nortriptyline, desipramine, and imipramine) is roughly similar [1••,15].
Standard dosage	Dosing should begin at 10 to 25 mg at bedtime. Dosing is increased slowly by 10 to 25 mg increments every 1 to 2 weeks up to 100 to 150 mg at bedtime, as tolerated and required to control symptoms.
Contraindications	Drug sensitivity, cardiac arrhythmias, congestive heart failure, recent myocardial infarction, narrow angle glaucoma, urinary retention from prostatic hypertrophy, or other causes.
Main drug interactions	Concurrent use of central nervous system depressants or anticholinergic agents.
Main side effects	Dry mouth, sedation, urinary retention, cardiac arrhythmias, orthostatic hypotension, dizziness, constipation, and weight gain. Secondary amines (nortriptyline, desipramine) have less sedating and anticholinergic activity than other drugs in this class.
Special points	As is true for most agents, the use of tricyclic antidepressants in neuropathic pain is off-label. In elderly patients, initiating treatment at a dose of 10 mg at bedtime may be better tolerated. Tricyclic antidepressants may be useful in combination with other agents.
Cost/cost effectiveness	Amitriptyline 25-mg tablets (90 tablets) cost $10.80; nortriptyline 25-mg tablets (90 tablets) cost $18.06; desipramine 25-mg tablets (180 tablets) cost $21.65; imipramine 25-mg tablets (90 tablets) cost $17.88.

Carbamazepine

	Carbamazepine is a first-generation anticonvulsant that modulates voltage-gated sodium channel activity and has a minor antagonistic effect at calcium channels. It is structurally similar to tricyclic antidepressants. It has been used effectively in a number of neuropathic pain states including diabetic neuropathy [11, Class I] and trigeminal neuralgia.
Standard dosage	Dosing should begin at 100 to 200 mg twice daily, increasing by 100 to 200 mg increments to a target dose of 200 to 400 mg three to four times a day. Serum levels should be monitored for doses of 600 mg a day or greater. Extended-release forms can be substituted once a maintenance dose is determined.
Contraindications	Drug sensitivity, bone marrow depression, concurrent use of monoamine oxidase inhibitors (MAOIs).
Main drug interactions	Barbiturates, cimetidine, cisplatin, diltiazem, erythromycin, fluoxetine, isoniazid, ketoconazole, lithium, oral contraceptives, phenytoin, rifampin, theophylline, verapamil, and valproate.
Main side effects	Dizziness, drowsiness, nausea and vomiting, swelling, skin rash, leukopenia, thrombocytopenia, hyponatremia, and hepatic dysfunction.
Special points	Carbamazepine is labeled for use in trigeminal neuralgia. Starting with 100-mg doses is better tolerated in the elderly. Complete blood counts and liver function tests should be checked at drug initiation and at least once during the first few months of therapy.
Cost/cost effectiveness	100-mg tablets (60 tablets) cost $12.20.

Gabapentin

	Gabapentin is now the most widely used anticonvulsant for neuropathic pain. It has several proposed modes of action, including increasing brain GABA levels and binding to the $\alpha\delta 2$ subunit of voltage-gated calcium channels. In a double blinded, placebo-controlled trial, gabapentin demonstrated efficacy in the treatment of painful diabetic neuropathy at a dose of 3600 mg per day [10•, Class I]. Doses below 1800 mg per day are less likely to be effective. In comparative studies, gabapentin is as or more effective than amitriptyline in painful diabetic neuropathy [16].

Standard dosage	Gabapentin can generally be initiated at a dose of 300 mg three times daily. In some circumstances, beginning at 300 mg nightly is advisable. Dosing should be titrated as needed and tolerated by 300-mg increments every week to a target of 900 mg to 1200 mg three times daily. Higher doses can be used safely, but single doses should not exceed 1200 mg, and the frequency of dosing must be increased to a four or five-time-per-day regimen.
Contraindications	Prior hypersensitivity.
Main drug interactions	Drug interactions are relatively trivial. Cimetidine alters the renal excretion of gabapentin. Bioavailability is reduced by concomitant use of magnesium or aluminum-based antacids.
Main side effects	Sedation, fatigue, dizziness, confusion, tremors, weight gain, peripheral edema, and headache.
Special points	In general, gabapentin is better tolerated than other anticonvulsants, and its favorable side effect profile has made it a popular choice in the treatment of neuropathic pain.
Cost/cost effectiveness	300-mg capsules (90 capsules) cost $105.12.

Lamotrigine

	Lamotrigine is a novel anticonvulsant that stabilizes the slow inactivated conformation of a subtype of sodium channels. It may also inhibit the release of neurotransmitters including glutamate. Although data from well-designed studies in neuropathic pain are conflicting, lamotrigine was recently found to be effective in a randomized, double blinded, placebo-controlled trial of 59 patients with painful diabetic neuropathy [17, Class I]. Doses of 200 mg per day and greater were effective.
Standard dosage	Dosing begins at 25 mg nightly or twice per day and continued for 2 weeks. The dose is increased slowly be 25-mg increments weekly to a target of 100 to 200 mg twice daily.
Contraindications	Hypersensitivity.
Main drug interactions	Valproic acid, phenytoin, and carbamazepine.
Main side effects	Mild to serious rashes including Stevens-Johnson syndrome, dizziness, unsteadiness, drowsiness, and diplopia.
Special points	Rashes are more common in children and with faster titration schedules. At the first sign of drug-related rash, lamotrigine should be discontinued. Maintenance doses with concomitant valproic acid are lower, in the range of 100 to 150 mg per day in two divided doses.
Cost/cost effectiveness	25-mg tablets (60 tablets) cost $129.60.

Topiramate

	Neuropathic pain studies of this novel anticonvulsant are in the initial stages. It has been effective in open-label studies of refractory neuropathic pain and in a preliminary report of a small, randomized, double blinded, placebo-controlled study in diabetic neuropathy [18, Class I (preliminary)]. Topiramate can cause weight loss, a potential advantage in the management of diabetic patients who are overweight. Topiramate has multiple mechanisms of action that may relate to its analgesic effect. These include blockade of voltage-gated sodium and calcium channels, inhibition of glutamate receptors, and modulatory effects on GABA receptors.
Standard dosage	Dosing begins at 25 to 50 mg at bedtime for a week, increasing by 25 to 50 mg increments on a weekly basis up to 200 mg twice daily.
Contraindications	Hypersensitivity and concomitant use of other carbonic anhydrase inhibitors.
Main drug interactions	Carbamazepine, phenytoin, valproic acid, oral contraceptives, and digoxin.
Main side effects	Psychomotor slowing, confusion, fatigue, weight loss, kidney stones, paresthesias, acute myopia, and secondary angle closure glaucoma.
Special points	Patients should be advised to maintain adequate fluid intake to minimize the risk of kidney stone formation.
Cost/cost effectiveness	25-mg tablets (60 tablets) cost $76.11.

Tramadol

	Tramadol, an analgesic medication with monoaminergic and opiate activity, has been effective in blinded, placebo-controlled studies of diabetic neuropathy and other forms of painful polyneuropathy [12,13•, Class I].
Standard dosage	Dosing usually begins at 50 mg two times per day. The dose can be titrated upwards slowly at increments of 50 mg every 3 to 7 days, using a three or four times daily schedule. The maximum recommended daily dose is 100 mg four times a day.
Contraindications	Previous hypersensitivity to opioid analgesics. It should be avoided in the setting of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs.
Main drug interactions	Increased risk of central nervous system (CNS) depression or seizures has been described with concurrent use of other centrally acting drugs including neuroleptics and all major families of antidepressants. Other potential drug interactions include carbamazepine, digoxin, and warfarin.
Main side effects	Sedation, dizziness, constipation, headache, nausea, and vomiting.
Special points	The abuse potential of tramadol appears to be low, but this agent is best avoided in patients with a prior history of addiction. Because tramadol undergoes hepatic metabolism and is partially excreted unchanged in the urine, dosing should be reduced in patients with either hepatic (maximum dose of 50 mg twice a day) or renal insufficiency (maximum dose of 100 mg twice a day).
Cost/cost effectiveness	50-mg tablets (30 tablets) cost $26.33.

Mexiletine

	Mexiletine, an oral analogue of lidocaine that similarly blocks sodium channels, has demonstrated mixed results in placebo-controlled studies of diabetic and HIV-related neuropathies [1••,19–21, Class I]. Mexiletine's main use is as a class 1B anti-arrhythmic. Many patients find this agent difficult to tolerate.
Standard dosage	The recommended starting dose is 150 mg per day. The dose is increased in 150-mg increments every 7 days to a maximum of 10 mg/kg per day, given on a three times per day basis. Doses should not exceed a daily dose of 900 mg. Plasma levels can be measured. Levels greater than 2.0 μg/mL are associated with a greater frequency of adverse events.
Contraindications	Preexisting second or third-degree atrioventricular blockade, cardiogenic shock.
Main drug interactions	Theophylline, phenytoin, rifampin, phenobarbital, and cimetidine.
Main side effects	Nausea, vomiting, dizziness, tremor, nervousness, headache, and liver function abnormalities.
Special points	Mexiletine should be taken with food, because nausea is a major side effect. Patients with a prior cardiac history or cardiac symptoms should be medically cleared before mexiletine is initiated for pain.
Cost/cost effectiveness	150-mg capsules (90 capsules) cost $34.21.

Opioids

	Controlled data on the use of opioids for neuropathic pain is lacking. Because of the high incidence of side effects and potential for abuse, chronic opioids should be reserved for refractory patients [22••]. Longer-acting agents are preferred, including extended-release oxycodone or morphine and methadone. The chronic use of opioids in neuropathic pain can be justified if other avenues of therapy have failed, pain relief enhances overall functioning, and close monitoring is feasible.
Standard dosage	There is no standard dosage. The dose should be slowly titrated until there is pain relief and improvement in function. Effective daily doses may be relatively low: 30 to 60 mg per day for extended-release oxycodone and 1 to 15 mg per day for methadone.
Contraindications	Hypersensitivity, significant respiratory depression or obstructive pulmonary disease, paralytic ileus, and intolerance.
Main drug interactions	Central nervous system depressants.
Main side effects	Respiratory depression, constipation, nausea, vomiting, sedation, dizziness, and asthenia.

Special points	Patients should be advised of the potential for drug tolerance. Tolerance and addictive behavior have been uncommon in the experience of specialists using chronic opioids in this clinical setting [22••].
Cost/cost effectiveness	No data available.

Topical agents

Capsaicin

	Capsaicin, an alkaloid extracted from chili peppers that depletes substance P from sensory nerves, has had a significant effect on neuropathic pain in a majority of studies of diabetic neuropathy [1••,14, Class I]. The burning sensation induced during early phases of treatment has raised concerns about inadequate blinding in studies. The one study that used a burning vehicle as a control failed to demonstrate a positive effect for capsaicin [23].
Standard dosage	0.075% capsaicin cream is applied to the painful area three to four times daily.
Contraindications	Prior hypersensitivity to topical application or to hot peppers.
Main drug interactions	No significant interactions for topical use.
Main side effects	Transient burning, sneezing, coughing, and skin irritation and rash.
Special points	Capsaicin cream is available over-the-counter. The cream should be used in well-ventilated areas, and patients should avoid rubbing their eyes after use. Nonsteroidal anti-inflammatory agents may be added if the initial burning from capsaicin is intense. This side effect usually improves over several weeks.
Cost/cost effectiveness	15 pain-relief patches cost $10.99.

Lidocaine patch

	A 5% lidocaine patch has been approved by the US Food and Drug Administration (FDA) for treatment of post-herpetic neuralgia, based on double blinded, placebo-controlled data [24, Class I].
Standard dosage	Dosing begins with one patch applied to intact skin for up to 12 hours of a 24-hour period. The number of patches can be increased to a maximum of three applied for 12 hours of a 24-hour period. Patches cannot be reused.
Contraindications	Prior hypersensitivity to local amide anesthetics.
Main drug interactions	Lidocaine patches should be used with caution in patients receiving antiarrhythmic or local anesthetic drugs.
Main side effects	Local skin erythema or edema.
Special points	Patches can be cut to conform to a desired area prior to removal of the release liner. Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine.
Cost/cost effectiveness	No data available.

Interventional procedures

- There are a wide variety of interventional therapies for painful peripheral neuropathy. In general, these approaches are reserved for patients who have failed a number of aggressive trials using oral or topical agents. Interventional techniques include local anesthetic blocks, acupuncture, percutaneous as well as implanted spinal cord stimulators, and implanted intrathecal catheters for delivery of opiates, local anesthetics, and antispasticity agents.
- Interventional therapies are best performed by physicians with specialized skill who are familiar with and are able to manage potentially serious adverse events, which can include respiratory depression and apnea from intrathecal drug delivery. These techniques are mainly available through anesthesiologist-staffed pain clinics.

- Clinical efficacy for interventional procedures is generally based on Class II and III evidence and is not universally accepted.

Acupuncture

	Efficacy has been claimed for acupuncture in several studies of chronic pain, including painful diabetic neuropathy with some 75% of patients showing a favorable response [25, Class III]. However, nearly all acupuncture trials in chronic pain have methodologic limitations including small sample sizes and inadequate controls for the nonspecific effect of acupuncture. Certainly, designing a placebo arm for an acupuncture study is a challenging task. When a standardized acupuncture regimen was evaluated in painful HIV-related peripheral neuropathy that used three control points on the calf as the placebo arm, there was no analgesic advantage for acupuncture over the control point insertions at either the 6- or 14-week time points [26]. The investigators did raise the possibility that the control point insertions may have had an analgesic effect and did not represent a true, inert control.
Standard procedure	Acupuncture regimens are largely individualized in practice. One to three acupuncture treatments per week is a typical schedule. Acupuncture points corresponding to those used in traditional Chinese medicine are usually chosen.
Contraindications	Essentially none.
Complications	Essentially none. There is a minimal risk of bleeding and skin infection. Occasional patients (less than 5% in published series) find the procedure uncomfortable and cannot tolerate it.
Special points	Acupuncture variations include the application of heat or an electrical current to the stainless steel needles.
Cost/cost effectiveness	The charge for each sesson is approximately $85.

Spinal cord stimulators

	Approximately 50% of patients with neuropathic pain from diabetes, postherpetic neuralgia, and other etiologies that are refractory to conventional therapies have a long-term response to spinal cord stimulation [27,28, Class II and III].
Standard procedure	Pulse widths range from 50 to 1000 microseconds at a preferred frequency of 50 to 120 Hz and stimulation intensity of 0 to 10 volts.
Contraindications	Concurrent use of anticoagulants.
Complications	Tolerance over time, wound infection, lead migration.
Special points	After the epidural electrode is placed, an external stimulator is used to ensure that the patient has a favorable response over a trial period of 3 to 7 days. Implantation of a permanent internal device can proceed in those patients who report a satisfactory response (*ie,* a 50% or greater reduction in pain intensity).
Cost/cost effectiveness	The stimulator costs approximately $2000. Implantation costs approximately $1500.

Percutaneous stimulators

	Percutaneous electrical nerve stimulation (PENS) is a relatively novel analgesic approach that combines the advantages of transcutaneous stimulation and electroacupuncture. Multiple acupuncture-like needle probes are inserted into the painful area and then connected to a low-output electrical source. In a recent, investigator-blinded crossover study of 50 patients with painful diabetic neuropathy, pain scores, physical activity, and sleep quality improved with PENS treatment compared with baseline values [29, Class II]. No significant change was seen following sham treatments. The treatment effect is short-lived, however, and the response to long-term therapy was not studied.
Standard procedure	Treatment initiation usually begins with two to three sessions a week. Stimulation frequencies are typically 15 to 30 Hz with a maximal current of 25 mamps and pulse width of 0.5 msec.
Contraindications	Essentially none.
Complications	Essentially none. There is a minimal risk of bleeding and skin infection with needle insertion.

Special points Percutaneous electrical nerve stimulation has decreased the daily oral analgesic requirements in a number of chronic pain states. Based on current studies, it should be viewed as an adjunctive, and not primary, therapy.

Cost/cost effectiveness sessons cost approximately $85 each.

Assistive devices

Transcutaneous stimulation

Transcutaneous electrical stimulation (TENS) is widely used in neuromuscular and pain syndromes, although its efficacy is actively debated. Response to this noninvasive technique varies significantly between studies and patients. In a trial of painful diabetic polyneuropathy in which the investigators blinded the subjects as to whether they received active or sham electrodes, both groups exhibited a significant decline in pain scores, although the magnitude of improvement and the percentage of patients responding were greater in the active electrode arm [30]. When the sham group crossed over to active therapy, their pain scores decreased significantly [Class II].

Standard procedure Treatment with TENS units generally begins daily, with stimulation sessions lasting 30 minutes or longer. Over time, one can reduce the frequency of treatment sessions, although the analgesic effect is transient, and the procedure needs to be repeated at least every few weeks.

Contraindications None.

Complications Essentially none. Some patients find it difficult to tolerate the surface stimulation due to allodynia.

Special points Individual adjustments of the pulse waveform, duration, frequency, and voltage are required to maximize the clinical response.

Cost/cost effectiveness Basic TENS units range in cost from $700 to $900.

Magnetic therapy

Annual worldwide spending for magnetic devices to treat pain is estimated to be in the billions of dollars. Public acceptance of subthreshold magnetic devices is largely based on anecdotal statements, although rigorous trials are now being performed to test this alternative approach. A preliminary randomized, sham-controlled crossover study of magnetic insoles in peripheral neuropathic pain provides some basis for efficacy [31, Class III]. However, the study was small, diabetic patients responded far better than non-diabetics, and no group was ever assigned to sham magnets for both feet at the same time, complicating the analysis. Results from a larger, double blinded, placebo-controlled study of magnetic insoles in diabetic neuropathy are pending.

Standard procedure There are no standards.

Contraindications None.

Complications Essentially none. The uneven surface of some magnetic insoles may place neuropathy patients with foot ulceration or sores at risk.

Cost/cost effectiveness No data available.

Physical therapy and exercise

- Physical therapy and exercise may indirectly benefit patients with neuropathic pain. Muscle function and cardiovascular fitness can improve. Improving a patient's overall condition and well-being may enhance pain management efforts.
- Exercise is a key component of most weight-loss programs, an important factor for diabetics in controlling hyperglycemia.

- Physical therapy programs may include relaxation and stretching techniques that are beneficial.

Emerging therapies

- As our understanding of the mechanisms responsible for neuropathic pain expands, potential molecular targets also widen. New agents in clinical trials or under development include sodium channel blockers designed as analgesics, calcium channel blockers, NMDA antagonists, GABA agonists, inhibitors of inflammatory mediators and cytokines, and nerve growth factors.
- Although antidepressants with single modes of action, such as the selective serotonin reuptake inhibitors, have had mixed success in neuropathic pain, new agents with balanced inhibition of serotonin and norepinephrine offer theoretical advantages and are likely to be better tolerated than the tricyclics.
- The growing number of third generation anticonvulsants are likely candidates for neuropathic pain. Zonisamide, an anticonvulsant already on the market, and pregabalin, an anticonvulsant still under investigation, have shown promise in open-label and preliminary placebo-controlled studies.
- Tizanidine, a central a2-adrenoreceptor agonist marketed for spasticity that reduces the release of excitatory amino acids and substance P, has demonstrated efficacy in an open-label study.

Venlafaxine

Standard dosage	This antidepressant strongly inhibits the reuptake of both serotonin and norepinephrine, but has minimal muscarinic and histaminergic activity compared to tricyclic antidepressants and should be better tolerated by most patients. In a preliminary report, venlafaxine extended release was superior to placebo in the amelioration of pain in nondepressed patients with diabetic neuropathy at daily doses of 150 to 225 mg [32].
Contraindications	Prior hypersensitivity and concomitant use of MAOIs.
Main side effects	Nausea, dizziness, somnolence, insomnia, sexual dysfunction, and dry mouth.
Cost/cost effectiveness	No data available.

Pregabalin

Standard dosage	This investigational agent with GABAergic properties has demonstrated efficacy in a preliminary report of a double blind, placebo-controlled study in painful diabetic neuropathy [33]. Effective doses were 300 and 600 mg per day, and both pain and sleep interference improved.
Main side effects	Pregabalin has been well tolerated in studies. Dizziness and somnolence have been the most common adverse events.
Cost/cost effectiveness	No data available.

Tizanidine

Standard dosage	Dosing begins at 2 to 4 mg nightly, with weekly escalations of 2 to 4 mg until a favorable response or significant adverse events occur. The total dose can be given on a once daily to three times daily basis. Effective doses in an open-label study ranged from 6 to 36 mg daily [34, Class III]. The maximum recommended daily dose is 36 mg.
Contraindications	Prior hypersensitivity.
Main side effects	Dizziness, lightheadedness, hypotension, drowsiness, fatigue, and dry mouth.
Cost/cost effectiveness	2-mg tablets (90 tablets) cost $102.81.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Sindrup SH, Jensen TS: **Pharmacologic treatment of pain in polyneuropathy.** *Neurology* 2000, **55:**915–920.

The authors analyze data from doubleblinded, placebo-controlled pharmacologic trials in neuropathic pain. Using a numbers needed to treat methodology defined as the number of patients required to obtain one patient with at least 50% pain relief, comparisons are made between the different agents. Results from the analysis support the use of tricyclic antidepressants as first-line agents for neuropathic pain. Leading alternatives are gabapentin, tramadol, and carbamazepine.

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