Peripheral Neuropathic Pain Syndromes: Three Case Studies
Case Study and Commentary, Avi Ashkenazi, MD, and M. Alan Stiles, DMD

Chronic neuropathic pain is a problem commonly encountered in clinical practice. It has been estimated that there may be more than 3 million people with painful diabetic neuropathy in the United States [1] and up to 1 million with postherpetic neuralgia [2]. Chronic neuropathic pain causes psychological distress, physical disability, reduced quality of life, and increased health care costs [3,4].

Neuropathic pain is often described as burning, shooting, or electric shock–like in character. It typically has a constant component on top of which paroxysms of shooting pain may occur. Cutaneous allodynia is a frequently associated symptom, as are paresthesias, hyperalgesias, and dysesthesias. Examination may reveal sensory deficits in a peripheral nerve or in a radicular distribution. The causes of neuropathic pain are numerous and include infections, inflammatory diseases, metabolic abnormalities, trauma, nerve compression or entrapment, toxin or drug exposure, and tumors (Table 1).

CASE ONE
Initial Presentation
Grade 60-year-old man presents to his primary care physician complaining of a sharp pain in his left jaw typically occurring when he chews food. He states that the attacks are severe and last a few seconds.

History
The pain began 4 years ago but is intermittent, remitting for weeks to months at a time. The pain is triggered by chewing or sometimes when the left lower face is brushed lightly. The patient had his dentures remade in an attempt to alleviate the problem, but there has been no change in his symptoms.

Physical Examination
Intraoral examination reveals complete upper and lower dentures with completely normal mucosa. Neurologic examination is normal. A magnetic resonance imaging (MRI) scan of the brain and course of the trigeminal nerve is ordered, and the results are normal.

From Thomas Jefferson University Hospital, Philadelphia, PA.

Program Audience
Primary care physicians.

Educational Needs Addressed
Chronic neuropathic pain is a problem commonly encountered in clinical practice. It has been estimated that there may be more than 3 million people with painful diabetic neuropathy (PDN) in the United States and up to 1 million with postherpetic neuralgia (PHN). PHN is one of the most common and serious complications of herpes zoster. A variety of agents are used for treatment, but PHN is often refractory to these therapies. PHN often results in significant morbidity and health care resource use. PDN is a common complication of diabetes that can profoundly diminish quality of life. An estimated 20% to 24% of diabetics in the United States experience PDN. Trigeminal neuralgia is an extremely painful condition. Although current pharmacotherapy allows most patients some degree of comfort, a substantial number do not have adequate pain management. Education, patient support, and reassurance are important components of treatment of these common and potentially debilitating disorders.

Educational Objectives
1. Describe the epidemiology and impact on quality of life of trigeminal neuralgia (TN), postherpetic neuralgia (PHN), and painful diabetic nephropathy (PDN)
2. Specify the approach to drug therapy for TN, PHN, and PDN
3. Describe surgical treatments available for TN

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CME jointly sponsored by Boston University School of Medicine and JCOM
What is trigeminal neuralgia?

Trigeminal neuralgia is a severe, almost exclusively unilateral neuropathic pain located within the distribution of the trigeminal nerve, manifesting as paroxysmal, high-intensity jabs or stabs that last for seconds. Each attack may be followed by a refractory period, a period of relief that lasts minutes to hours. The burst of pain can occur spontaneously or can be triggered by stimulating a specific area of the trigeminal dermatome known as the trigger zone. Trigger zones can be difficult to locate. They exist anywhere within the trigeminal distribution, including intraorally. The trigger zone is generally in the same division of the trigeminal nerve as the pain. For this reason, patients characteristically avoid touching the face, washing, shaving, brushing the teeth, biting or chewing, or any other maneuvers that stimulate the trigger zones and produce the pain [5]. This avoidance is an invaluable clue to the diagnosis. In almost every other facial pain syndrome, patients massage, abrade, or apply heat and cold to the painful area. The pain is often likened to an "electric shock" and is typically accompanied by a unilateral grimace, hence the designation "tic douloureux." The pain may occur daily for weeks or months and then cease, sometimes for years, before returning.

A classification that has recently been challenged is that of typical versus atypical trigeminal neuralgia. In typical trigeminal neuralgia, the patient is pain-free between paroxysms; in atypical trigeminal neuralgia, aching or burning background pain occurs between attacks. Based on clinical observations, however, it has been suggested that atypical trigeminal neuralgia often evolves from typical trigeminal neuralgia [6].

What causes trigeminal neuralgia?

Trigeminal neuralgia had been previously classified as either idiopathic or secondary. Since a majority of cases of "idiopathic" trigeminal neuralgia are currently considered to be caused by compression of the trigeminal nerve root by a blood vessel, the secondary form is predominant [7]. Lesions in the posterior fossa, such as meningioma, vestibular schwannoma, epidermoid cyst, basilar artery aneurysm, and pontine infarction, can cause trigeminal neuralgia [8]. Neoplasms involving the trigeminal nerve generally produce constant neuropathic pain associated with sensory loss. Trigeminal neuralgia is also associated with multiple sclerosis (MS), when a demyelinating plaque is located at the trigeminal root entry zone in the pons. Trigeminal neuralgia can occur as the first manifestation of MS, but this is rare. Most patients who have trigeminal neuralgia in association with MS have significant neurologic signs of MS for many years before the facial pain begins. Patients with MS are more likely to have bilateral trigeminal neuralgia than patients without MS.

What is the diagnostic evaluation for patients with trigeminal neuralgia?

Although the diagnosis remains based on history and symptomatology, imaging techniques such as MRI and magnetic resonance angiography may be useful in identifying blood vessels that compress the trigeminal nerve and ruling out tumors, aneurysms, and other structural lesions. There is general agreement that patients with trigeminal neuralgia and sensory loss should undergo neuroimaging. Some authorities, however, recommend performing high-resolution, contrast-enhanced MRI in all patients with trigeminal neuralgia to rule out secondary causes [9].

What medications are available for treatment?

Initial management of trigeminal neuralgia is medical [10,11] (Table 2). Surgical therapy should be considered if medical treatment fails or cannot be tolerated. The medical treatment of trigeminal and other cranial neuralgias is based on the capacity of the drugs employed to decrease nerve hyperexcitability, either peripherally or centrally. Generally, treatment is begun with a medication that has proven antineuralgic properties. Initial doses are low and gradually

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**Table 1. Common Causes of Neuropathic Pain**

<table>
<thead>
<tr>
<th>Peripheral primary injury</th>
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</thead>
<tbody>
<tr>
<td>Diabetic neuropathy</td>
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<tr>
<td>Alcoholic neuropathy</td>
</tr>
<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy</td>
</tr>
<tr>
<td>HIV-related neuropathy</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
</tr>
<tr>
<td>Posttraumatic neuralgias</td>
</tr>
<tr>
<td>Radiculopathy caused by spinal osteoarthritis or discopathy</td>
</tr>
<tr>
<td>Postradiation plexopathy</td>
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</table>

<table>
<thead>
<tr>
<th>Central primary injury</th>
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</thead>
<tbody>
<tr>
<td>Thalamic stroke</td>
</tr>
<tr>
<td>Compressive myelopathy</td>
</tr>
</tbody>
</table>

titrated with close clinical monitoring until maximum tolerated dose or pain-free dose is reached. Since the natural course of trigeminal neuralgia may include spontaneous remissions, an attempt to gradually reduce the dose should be made if the patient has been pain-free for more than 4 to 6 weeks. However, the physician should be alert to the possibility of pain recurrence. The aim should be to control the pain with one drug; however, occasionally polypharmacy is required. The choice of drug is based on data available on efficacy and side effect profile.

For years, the gold standard for treatment has been carbamazepine, given at a dose of 100 to 200 mg 2 to 3 times daily. Carbamazepine is initially effective in approximately 75% of patients. Response to carbamazepine has been described by some as almost diagnostic. Potential side effects include drowsiness, dizziness, nausea, vomiting, ataxia, granulocytopenia, impaired liver function, and hyponatremia. Serum drug levels, complete blood count, liver function tests, and blood sodium should be monitored. Carbamazepine may also cause various skin reactions, including Stevens-Johnson syndrome. The chemically related drug oxcarbazepine can also be used for trigeminal neuralgia, with fewer side effects. The risk of hyponatremia, however, is the same as with carbamazepine.

If symptoms persist while the patient is taking an adequate dose of carbamazepine, another drug should be added to the regimen. Generally, baclofen is employed, beginning with 10 mg daily and increasing to 60 mg to 80 mg daily in divided doses. An important side effect is drowsiness, especially if the drug is titrated up quickly. Baclofen treatment should be discontinued very gradually, by no more than 5 to 10 mg per week. If it is tapered off rapidly, hallucinations, anxiety, and seizures may occur. If the pain persists, a third drug, such as phenytoin, may be added or substituted. Phenytoin dosage is 300 to 500 mg daily. Side effects include drowsiness, ataxia, hirsutism, gum hyperplasia, hepatotoxicity, and allergic skin reactions. It is initially effective in 60% of patients.

Clonazepam is used occasionally in the treatment of trigeminal neuralgia, but drowsiness is a limiting side effect in many patients. Starting dose is 0.5 mg before bedtime, which can be increased as tolerated up to 6 mg/day. Lamotrigine, at a dose of 400 mg/day, was found to be superior to placebo in a study of trigeminal neuralgia treatment [12]. A major concern with this drug is the potential development of a skin rash that may be severe and even fatal (Stevens-Johnson syndrome and toxic epidermal necrolysis). The risk for this complication is thought to be lower if the drug is started at a low dose (25 mg/day) and titrated up slowly (by no more than 25 mg every week) to the effective dose. There are anecdotal reports on the efficacy of gabapentin and topiramate in the treatment of trigeminal neuralgia [12–14] (Table 2). Non-steroidal anti-inflammatory drugs or opioids have no established role in the treatment of trigeminal neuralgia.

**Treatment in This Patient**

The patient was prescribed carbamazepine. He initially had some relief, but after a few months the pain reemerged. The carbamazepine dosage was increased, and the patient became virtually pain-free on the higher dose. However, he experienced dizziness, and because he works as a contractor the dizziness was an unacceptable side effect.

### Table 2. Drug Therapy for Trigeminal Neuralgia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>400–1200 mg</td>
<td>Drowsiness, dizziness, ataxia, leukopenia</td>
<td>Monitor drug serum levels, CBC, LFTs</td>
</tr>
<tr>
<td>Baclofen</td>
<td>40–80 mg</td>
<td>Drowsiness, dizziness</td>
<td>Taper off gradually</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>300–500 mg</td>
<td>Cognitive impairment, ataxia, hirsutism</td>
<td>May be given intravenously as acute therapy. Monitor drug serum levels, CBC, LFTs.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>150–400 mg</td>
<td>Skin rash, dizziness, diplopia</td>
<td>Titrate daily dose up slowly</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900–2400 mg</td>
<td>Fatigue, drowsiness</td>
<td>Potential risk of severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis).</td>
</tr>
<tr>
<td>Topiramate</td>
<td>200–300 mg</td>
<td>Paresthesias, cognitive impairment, weight loss</td>
<td>Adequate hydration to prevent renal calculi</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1.5–6 mg</td>
<td>Drowsiness, fatigue, dizziness</td>
<td>Start at 1 mg/day and titrate dose up slowly</td>
</tr>
</tbody>
</table>

CBC = complete blood count; LFTs = liver function tests. (Adapted with permission from Ashkenazi A, Levin M. Three common neuralgias: how to manage trigeminal, occipital, and postherpetic pain. Postgrad Med 2004;116(3):16–32, 48.)
patients who have trigeminal neuralgia will not respond or become unresponsive to medical therapy and will need some form of neurosurgical treatment (Table 3). The type of operation performed varies widely among institutions. Patients need to be completely and clearly apprised of the nature of the operations proposed, the procedures to be undertaken, possible side effects, costs, morbidity, and mortality.

Selective percutaneous lesioning of the trigeminal root using a radiofrequency electrode placed in the root under radiographic control (radiofrequency rhizotomy/gangliolysis) is an operative procedure that has gained wide acceptance [15]. It has the advantages of safety and simplicity. The anesthesia used is light; the patient is awake during some of the procedure, recovers rapidly, and is often found eating supper a few hours after the operation has been completed. The patient can be discharged from the hospital the same or the next day. However, occasional corneal anesthesia occurs, and uncomfortable dysesthesias or jaw weakness can occur. Altered sensation in the face is reported by many patients, but only a few are bothered by it. At present, there has been no mortality associated with this procedure.

A variation on this procedure is percutaneous retrogasserian rhizolysis with glycerol [16]. Excellent responses to this procedure with only minimal disturbance of facial sensitivity have been reported [16]. The presumption is made that glycerol is neurotoxic, acts on partially demyelinated nerve fibers, and eliminates the compound action potentials in the trigeminal rootlets that are associated with pain. Although some neurosurgeons continue to favor percutaneous radiofrequency rhizotomy, the trend is towards glycerol rhizolysis of the trigeminal ganglion.

An alternative procedure is microvascular decompression of the trigeminal root [17]. Here, the neurosurgeon assumes that a lesion (usually an arterial loop) will be found compressing the trigeminal root near the brainstem. If and when it is found, the compressing lesion is lifted from the trigeminal root, often by interposing a sponge. By deduction, therefore, it is suggested that in most cases trigeminal neuralgia is a compressive cranial mononeuropathy. The surgery is successful and effective in elderly patients [18]. The major complications are cerebellar injury, hearing loss, and cerebrospinal fluid leak. The length of stay in the hospital is not influenced by the age of the patient.

There are significant differences in costs between these various operations. Radiofrequency lesions and glycerol injections are done rapidly, and the patient is almost always quickly discharged. When microsurgical decompression of the trigeminal root is performed, a formal craniotomy is required, and the patient often spends 4 to 10 days in the hospital and a similar period of time in convalescence. The percutaneous denervation is less likely than microvascular decompression to cause death, stroke, facial weakness, or hearing loss, but it is more likely to be associated with recurrence or dysesthesias [19].

Meglio and Cioni have described a new percutaneous microcompression of the trigeminal ganglion as a variation on the usual surgical techniques [20]. They employ a small balloon, filled to about 1 mL, which is introduced by percutaneous means through the foramen ovale and inflated against the ganglion for periods ranging from 1 minute to 10 minutes. The results are in the range of 90% improvement in pain and compare favorably with other standard neurosurgical procedures. In effect, this is a variation on older concepts of compressing the trigeminal ganglion to relieve pain.

More recently, stereotactic radiosurgery with the gamma knife under local anesthesia has been used to treat patients with recurrent trigeminal neuralgia after unsuccessful medical or surgical management [21]. Being the newest procedure, the long-term data regarding side effects and outcome are not available; however, evidence to date suggests that it is a safe and effective method for treatment of trigeminal neuralgia.

Nerve block using 4% tetracaine dissolved in 0.5% 

### Table 3. Surgical Treatments for Trigeminal Neuralgia

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Efficacy</th>
<th>Recurrence Rate</th>
<th>Risks</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiofrequency gangliolysis</td>
<td>+++</td>
<td>Low</td>
<td>Corneal anesthesia</td>
<td>Most commonly used nonoperative procedure</td>
</tr>
<tr>
<td>Glycerol rhizolysis</td>
<td>++</td>
<td>Moderate</td>
<td>Corneal anesthesia</td>
<td>Requires general anesthesia</td>
</tr>
<tr>
<td>Trigeminal ganglion balloon compression</td>
<td>++</td>
<td>Moderate</td>
<td>Corneal anesthesia</td>
<td></td>
</tr>
<tr>
<td>Gamma knife radiosurgery</td>
<td>++</td>
<td>Low</td>
<td>Minimal at short term, but long-term risks are unknown</td>
<td>Long latency to pain relief</td>
</tr>
<tr>
<td>Microvascular decompression</td>
<td>+++</td>
<td>Low</td>
<td>Cranial nerve palsies; stroke and death (rare)</td>
<td>The only definitive therapeutic procedure available</td>
</tr>
</tbody>
</table>

bupivacaine has been reported to be effective in older patients who do not want surgical treatment [22].

**Follow-up**

Due to the unacceptable side effects, the patient was switched to oxcarbazepine, which was titrated to an effective dose. The patient has remained pain-free over the past 3 months on this regimen.

**CASE TWO**

**Initial Presentation**

A 70-year-old man presents to his primary care physician with a complaint of severe persistent pain in his right chest and back.

**History and Physical Examination**

The patient reports a rapid onset of right-sided back pain 4 months prior to his office visit. The pain radiated forward to the chest. Two days after pain onset, he noticed a skin eruption in a belt-shaped area at the level of the nipple on the right side, extending from the back to the anterior chest. The rash was initially maculopapular and progressed later to clusters of clear vesicles. He was diagnosed as having acute herpes zoster (“shingles”). No antiviral therapy was given. The vesicles gradually underwent crusting and healed over a period of 2 weeks, leaving areas of hyperpigmentation. The pain, however, persisted. He describes the pain as a constant aching and burning sensation, on top of which he has paroxysms of severe electric shock–like pain that last a few seconds. He tells his doctor that touching the affected skin provokes extreme pain and that he can not bear even the contact of his clothing with it. His sleep is severely disrupted due to the pain. His past medical history is unremarkable.

On examination, the patient is in obvious distress from pain. There is an area of scarring and hyperpigmentation at a right T4 dermatomal distribution. Light touch applied with a gauze pad to the affected area provokes intense pain. There are no other abnormal physical or neurologic findings.

**What is the diagnosis?**

This patient has postherpetic neuralgia (PHN). PHN is defined as pain that persists more than 3 months after healing of the zoster rash [23]. PHN is a common medical problem and is considered the most common complication of herpes zoster. The overall risk of developing PHN after acute herpes zoster is estimated at 9% to 34%, but it rises sharply with increasing age and reaches 73% in untreated patient older than 70 years [24,25]. Since the annual incidence of herpes zoster also rises with advanced age (to 10/1000 in people older than 80 years), PHN is an especially important health problem in the geriatric population. PHN results from peripheral nerve injury that occurs during reactivation of latent varicella zoster virus infection in dorsal root ganglia.

**What pharmacologic agents are available for the treatment of PHN?**

Drug therapy for PHN may be given either topically or systemically (Table 4). Three agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of PHN: topical lidocaine, topical capsaicin, and gabapentin.

### Table 4. Pharmacologic Treatment of Postherpetic Neuralgia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine 5% patch</td>
<td>Up to 3 patches for 12 h</td>
<td>Possible local irritation</td>
<td>Apply to intact skin only; high cost</td>
</tr>
<tr>
<td>Capsaicin cream</td>
<td>Apply 3–4 times/day</td>
<td>Burning sensation before analgesia</td>
<td>Apply to intact skin only; NNT = 5.3</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1800–3600 mg (in 3 divided doses)</td>
<td>Dizziness, somnolence</td>
<td>Usually well-tolerated; NNT = 3.2</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10–200 mg (one dose before bedtime if dose is ≤ 25 mg/day; 2–3 divided doses for higher daily doses)</td>
<td>Sedation, confusion, urinary retention, orthostatic hypotension, dry mouth, arrhythmias</td>
<td>Start at a low dose and titrate up gradually; NNT = 2.3</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25–150 mg (dosing schedule as for amitriptyline)</td>
<td>Same as for amitriptyline but less severe and less frequent</td>
<td>Start at a low dose and titrate up gradually; NNT = 2.3</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 mg (5 mg q 6 h; 10 mg q 12 h for the CR preparation [OxyContin])</td>
<td>Sedation, dizziness, constipation</td>
<td>Potential, addiction, drug abuse and tolerance; NNT = 2.5</td>
</tr>
</tbody>
</table>

Neutral agents have the advantage of not causing sedation, a common side effect of systemic agents given for this disease, especially in the elderly.

Topical lidocaine, administered as a 5% patch or a 5% gel, significantly reduces the pain of PHN [26]. It should be applied to intact skin only. Up to 3 patches can be used at a time for a maximum of 12 hours/day. The efficacy and safety of topical lidocaine make it a first-line treatment choice for PHN. A disadvantage of topical lidocaine is its high cost compared with other agents used for this indication. Capsaicin is derived from red chili pepper and affects pain transmission by acting on neuronal vanilloid receptors [27]. Capsaicin cream (0.025% or 0.075%) is effective in the treatment of PHN. However, the initial burning sensation and hyperalgesia are intolerable to 30% of patients. It may take 2 to 4 weeks for the drug to achieve maximal effect. Capsaicin’s analgesic effect lasts 3 to 6 hours; therefore, it has to be applied 3 to 4 times daily. As with topical lidocaine, capsaicin should be applied to intact skin only. The cost of capsaicin cream is significantly lower than that of topical lidocaine.

Gabapentin is the only drug approved by the FDA as a systemic treatment for PHN [28,29]. The starting daily dose is 300 mg, which is titrated up gradually to the recommended daily dose of 1800 mg. The doses should be reduced and dosing intervals increased in patients with renal failure. The drug is usually well tolerated but side effects, such as dizziness and somnolence, may occur. Gabapentin has few drug-drug interactions, making it a good choice for patients who are already on multiple medications.

The tricyclic antidepressants are widely used for relieving PHN pain, and their efficacy for this indication has been established in well-designed trials [26,30]. Amitriptyline was shown to relieve PHN pain in 47% to 67% of patients. However, sedation, postural hypotension, and anticholinergic side effects may limit its use, especially in the elderly. The drug should be started at a low dose (10 to 25 mg/day), taken before bedtime, and increased gradually as tolerated to an effective dose (up to 150 mg/day). Nortriptyline has a similar efficacy to amitriptyline, with fewer anticholinergic side effects.

Patients with intractable PHN may benefit from opioid therapy [31]. Morphine, methadone, and oxycodone are all effective in relieving PHN pain. Treatment should be given according to established guidelines and the risks of addiction and abuse should be kept in mind [32,33].

- What are nonpharmacologic treatments for PHN?

Sympathetic nerve blocks have been used in the treatment of PHN. Although initial response rate is high, most patients do not achieve long-term pain relief [25]. There are also anecdotal reports on the efficacy of thalamic deep brain stimulation in relieving pain in refractory patients [24].

- Can PHN be prevented?

Early treatment of herpes zoster (starting within 72 hours of rash onset) with antiviral drugs has been shown not only to accelerate the resolution of acute pain but also to reduce the proportion of patients who will develop PHN [23,34]. The reduction in pain duration after treatment of herpes zoster with acyclovir is approximately twofold. Two other antiviral drugs, famciclovir and valacyclovir, are also effective in zoster-associated pain reduction. The benefit of treatment with antiviral agents for herpes zoster is most marked in patients older than age 50 years. The International Herpes Management Forum has recommended that patients with acute herpes zoster who present less than 72 hours after rash onset be treated with antiviral drugs for 7 days [23]. Corticosteroids have no proven efficacy in PHN prevention.

Follow-up

The patient was started on gabapentin 300 mg/day. The dose was increased gradually over 2 weeks to 1800 mg/day. After 4 weeks of therapy, the patient reported a significant pain relief. He also reported that the skin in the involved area was not as sensitive to touch as before treatment. He tolerated the treatment well, with only mild somnolence during the first 2 weeks of therapy that resolved subsequently.

CASE THREE

Initial Presentation

A 58-year-old woman presents with a complaint of tingling and pain in her feet that have increased in severity over the past year.

History

The patient has a 15-year history of type 2 diabetes mellitus for which she was placed on a comprehensive treatment program that includes a balanced diabetic diet, exercise, and an oral hypoglycemic drug (glyburide 2.5 mg/day). She admits that she has not been fully compliant with therapy. One year prior to her current presentation, she noticed tingling and numbness in both feet that became increasingly bothersome. Six months later she started suffering from pain in her feet that was particularly severe at night. She describes the pain as a constant aching and burning, with episodes of shooting pain superimposed on it. She took acetaminophen and aspirin for the pain in her feet, with no relief. Two weeks
prior to her visit she noticed an ulcer on her left ankle. She
also complains of the recent onset of tingling in her hands.
She complains that the contact of clothes or bedsheets with
the skin of her feet is painful. The patient also suffers from
hypertension, which is treated with lisinopril 20 mg/day.
She has no other symptoms.

**Physical Examination**

The patient is an obese woman in moderate distress from
pain. Blood pressure is 160/90 mm Hg. Cardiac examination
reveals an S3 sound. There is a shallow ulcer on her left ankle,
10 mm in diameter. Funduscopic examination shows micro-
anerysms and a few retinal exudates bilaterally. On neuro-
logic examination, sensation to pin prick, vibration, and posi-
tion is reduced in a glove-and-stocking distribution. There is
also a symmetric, mild (4+/5) weakness in the distal leg mus-
cles. Deep tendon reflexes are reduced in all 4 limbs and ankle
jers are absent. Romberg test is positive. A light brush of
the skin of the feet produces intense pain (cutaneous alldynia).

> Which clinical syndrome does this patient present with?

This patient presents with a typical clinical picture of diabet-
ic neuropathy, specifically the symmetric distal sensorimotor
type. This type is the most common of the peripheral neu-
ropathies associated with diabetes. Although a similar cli-
nical picture may be caused by a wide variety of diseases,
drugs, and toxins, diabetes is the most likely cause of neu-
ropathy in this patient.

Neuropathy is the most common complication of diabetes
and an important cause of morbidity and mortality in diabet-
ic patients [35]. The prevalence of peripheral neuropathy in
diabetic patients increases with the duration of disease and
can reach 50% in patients who have had diabetes for more
than 25 years [36]. Poor glycemic control is a risk factor for di-
betic neuropathy, as are cigarette smoking and dyslipidemia
[37]. In some patients, acute painful neuropathy may develop
shortly after initiation of insulin therapy (insulin neuritis) [38].
Diabetic neuropathy may affect any type of neuron in the
peripheral nervous system, including sensory, motor, and
autonomic. The sensory symptoms typically include numb-
ness, paresthesias, and pain. They usually progress from the
distal parts of the limbs proximally in a symmetric manner.
The pain has the typical characteristics of neuropathic pain
and may be associated with cutaneous allodynia.

> Which drugs can be used for the symptomatic treat-
ment of painful diabetic neuropathy?

Since there is no curative treatment for painful diabetic neu-
ropathy (PDN), control of pain is a major goal of therapy.
Various drugs have been used for this purpose, including
antidepressants, anticonvulsants, anti-arrhythmics, opioids,
tramadol, lidocaine, and capsaicin (Table 5) [39].

Amitriptyline, at doses of 25 to 150 mg/day, has a proven
efficacy in PDN pain relief [40]. It has been shown to cause
moderate or greater pain relief in 74% of patients, and was
equally effective in depressed and in nondepressed patients.
Sedation and anticholinergic side effects are of concern, espe-
cially in the elderly. Desipramine has similar efficacy to
amitriptyline in pain relief, with fewer side effects. Fluoxe-
tine, a selective serotonin reuptake inhibitor (SSRI), is not
more effective than placebo in the relief of PDN pain [40].
Paroxetine, however, given at a dose of 40 mg/day, was
found to be effective and well tolerated for PDN pain [41].
The efficacy of paroxetine in relieving neuropathic pain,
however, is lower than that of the tricyclic antidepressants.
The number needed to treat (NNT) to achieve pain reduction
of 50% in one patient with painful neuropathy was found to
be 6.7 for the SSRIs compared with 2.4 for the tricyclic anti-
depressants [42]. Recently, the nontricyclic antidepressant
bupropion was shown to be effective in pain reduction in
73% of 41 patients with various causes of neuropathic pain,
including PDN [43]. The drug was given at a daily dose of
150 to 300 mg and was well tolerated. It does not cause anti-
cholinergic effects or sedation but is hazardous in patients
with a history of seizures since it lowers the seizure thresh-
old. Venlafaxine, a serotonin-norepinephrine reuptake in-
hibitor, also has a proven efficacy in reducing PDN pain at
doses of 150 to 225 mg/day [35]. The drug may cause arter-
al hypertension, and blood pressure should be monitored in
patients treated with it. Other potential side effects include
anxiety, insomnia, anorexia, and dry mouth.

Duloxetine, a new antidepressant that affects both sero-
tonergic and noradrenergic neurotransmission, has recently
been approved by the FDA for the treatment of PDN [44].
The drug is given at a dose of 30 to 60 mg/day.

Of the anticonvulsants, gabapentin is as effective as ami-
triptyline in PDN pain relief and should be considered a
first-line agent for this indication [35]. The minimal effective
dose is 1600 mg/day; some patients may need a dose as high
as 3600 mg/day. The drug is generally well tolerated and
has few drug-drug interactions. The starting daily dose is
300 mg divided into 3 equal doses. It is then increased by
300 mg every other day to an effective dose in pain relief.

Carbamazepine was shown to decrease pain in 63% of
patients with PDN compared with 20% for placebo [39]. It is
not as effective as the tricyclic antidepressants for this indi-
cation and has multiple potential adverse effects, as men-
tioned above. Oxcarbazepine can also be used for this pur-
pose, with fewer side effects. More recently, the newer
Anticonvulsant lamotrigine at doses of up to 400 mg/day was shown to reduce PDN pain significantly more than placebo [45]. A major concern with this drug is the potential development of severe skin reactions.

Tramadol, an analgesic with combined opioid and serotonergic properties, was shown in controlled trials to be effective in PDN pain relief [46]. The effective dose is 200 to 400 mg/day and the main side effects are nausea and constipation. Oxycodone CR at a dose of 20 to 80 mg/day has been recently shown to relieve pain and disability in patients with PDN [47].

Intravenous lidocaine has been shown to alleviate PDN pain [39]. However, results with the anti-arrhythmic mexiletine, the oral analog of lidocaine, showed only modest pain relief. Topical treatments effective for PDN include capsaicin cream and lidocaine patch (Table 5).

In making the decision of which pharmacologic agent to use in a specific patient with PDN, the medical history should be reviewed, focusing on comorbidity and other drugs taken by the patient. There is strong evidence supporting the use of tricyclic antidepressants, gabapentin, tramadol, and capsaicin for this indication. Other agents, such as bupropion, venlafaxine, paroxetine, oxcarbazepine, lamotrigine, and opioids may be used alternatively. Careful monitoring of response to treatment and side effects is essential.

**What nonpharmacologic or complementary treatments may be beneficial for patients with PDN?**

Transcutaneous electrical nerve stimulation (TENS) has been studied as a treatment for PDN. It was shown as effective in the majority of patients, but pain recurred shortly after cessation of therapy. The treatment was well tolerated [48]. Cognitive behavioral therapy, acupuncture, magnet therapy, and laser therapy have also been used with some degree of success for the same purpose [39].

**What can be done to prevent, reverse, or slow the progression of PDN?**

The Diabetes Control and Complications Trial Research Group has shown that tight control of blood glucose levels in patients with type 1 diabetes reduces the risk for developing PDN by 60% over a period of 5 years [49]. Maintaining tight blood glucose level control can also prevent or slow the progression of neuropathy in patients who already have it. Pancreatic transplantation can cause an improvement in nerve conduction.

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**Table 5. Pharmacologic Treatment of Painful Diabetic Neuropathy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>25–150 mg</td>
<td>Sedation, confusion, urinary retention, orthostatic hypotension, dry mouth, arrhythmias</td>
<td>Start at a low dose and titrate up gradually</td>
</tr>
<tr>
<td>Desipramine</td>
<td>75–200 mg</td>
<td>Same as for amitriptyline but less severe and less frequent</td>
<td>Start at a low dose and titrate up gradually</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20–40 mg</td>
<td>Insomnia, sexual dysfunction, dizziness</td>
<td>Less effective than the TCAs for pain, but better tolerated</td>
</tr>
<tr>
<td>Bupropion</td>
<td>150–300 mg</td>
<td>Agitation, insomnia, anorexia, seizures</td>
<td>Avoid in patients with a history of seizures</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>150–225 mg</td>
<td>Nausea, sedation, dizziness, sexual dysfunction, hypertension</td>
<td>Monitor blood pressure</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30–60 mg</td>
<td>Nausea, sedation, dizziness, decreased appetite, constipation</td>
<td>FDA-approved for this indication</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1600–3600 mg</td>
<td>Dizziness, somnolence</td>
<td>Usually well-tolerated</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>400–1200 mg</td>
<td>Drowsiness, dizziness, ataxia, leukopenia</td>
<td>Monitor drug serum levels, CBC, LFTs</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>150–400 mg</td>
<td>Skin rash, dizziness, diplopia</td>
<td>Titrate dose up slowly</td>
</tr>
<tr>
<td>Tramadol</td>
<td>200–400 mg</td>
<td>Nausea, constipation, confusion, fatigue</td>
<td>Modest efficacy</td>
</tr>
<tr>
<td>Oxycodeone CR</td>
<td>10 mg q 12 h</td>
<td>Sedation, dizziness, constipation</td>
<td>Potential addiction, drug abuse, and tolerance</td>
</tr>
<tr>
<td>Lidocaine 5%</td>
<td>Up to 3 patches for 12 h</td>
<td>Possible local irritation</td>
<td>Apply to intact skin only</td>
</tr>
<tr>
<td>Capsaicin cream 0.025%–0.075%</td>
<td>Apply 3–4 times/day</td>
<td>Burning sensation before analgesia</td>
<td>Apply to intact skin only</td>
</tr>
</tbody>
</table>

CBC = complete blood count; LFTs = liver function tests; TCAs = tricyclic antidepressants.
study (NCS) results in parallel with the achievement of a durable normoglycemic state [36]. Aldose reductase inhibitors (ARIs) showed promise as neuroprotective agents in PDN in animal studies. This was recently confirmed clinically. A study that included 279 diabetic patients showed that the ARI fidarestat improved pain as well as NCS results [50]. Results with other ARIs, however, were disappointing. The antioxidant X-lipoic acid has also been recently studied for the prevention or amelioration of PDN symptoms. Given intravenously for 5 days and then orally at a dose of 600 mg/day or 1200 mg/day, X-lipoic acid improved in NCS results [51].

Follow-up

On laboratory examination, renal function was found to be mildly impaired. An electrocardiogram was obtained and showed normal sinus rhythm with moderate left ventricular hypertrophy. Her hemoglobin A\textsubscript{1c} was 9%. The patient was educated on the importance of losing weight, eating a balanced diet, and regular exercise. She was started on insulin therapy for a better control of blood glucose levels. Desipramine 25 mg/day was started as a symptomatic treatment for the pain in her feet. The dose was increased gradually over 3 weeks to 100 mg/day. She tolerated the treatment well and felt that the pain in her feet became milder. She still complained of bothering pain at night evoked by the contact of her feet with the bedsheets. Capsaicin cream was prescribed once a day before bedtime, with further improvement in pain and allodynia. At last follow-up, she had lost 20 lb, her blood glucose was well controlled, and the foot ulcer healed.

Summary

The management of patients with neuropathic pain should address both the pain itself and the psychological aspects associated with it. Treatment modalities include drugs, nerve blocks or stimulation, and, in refractory patients, ablative neurosurgical procedures. Education, patient support, and reassurance are important components of treatment of these common and potentially debilitating disorders. Careful pharmacologic management with consideration of the patient’s other diseases, concomitant medications, and previous drug history can result in symptomatic relief in most patients. Others may need more invasive procedures for the control of pain.

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References

Peripheral Neuropathic Pain Syndromes: Three Case Studies

DIRECTIONS: Each of the questions below is followed by 4 possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following statements regarding medical therapy for trigeminal neuralgia is FALSE?
   (A) Initial doses should be low and gradually titrated
   (B) It is preferable to begin therapy with a 2-drug regimen
   (C) Carbamazepine may cause Stevens-Johnson syndrome
   (D) Baclofen must be tapered slowly

2. Which of the following surgical treatments for trigeminal neuralgia is considered most efficacious?
   (A) Glycerol rhizolysis
   (B) Balloon compression
   (C) Gamma knife radiosurgery
   (D) Radiofrequency gangliolysis

3. Which of the following statements about topical lidocaine treatment for postherpetic neuralgia is FALSE?
   (A) 3 patches may be worn for up to 12 hours
   (B) High cost is a disadvantage
   (C) May cause sedation
   (D) Should be applied to intact skin

4. Which of the following is NOT a risk factor for painful diabetic neuropathy?
   (A) Poor glycemic control
   (B) Smoking
   (C) High cholesterol
   (D) NSAID use

5. Which of the following antidepressants has NOT been shown to be helpful for painful diabetic neuropathy?
   (A) Amitriptyline
   (B) Fluoxetine
   (C) Paroxetine
   (D) Duloxetine
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Circle your answer to the CME questions below:
1. A  B  C  D
2. A  B  C  D
3. A  B  C  D
4. A  B  C  D
5. A  B  C  D

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1. How would you rate this educational activity overall?
   _ Excellent  _ Good  _ Fair  _ Poor

2. Please rate the clarity of the material presented in the article.
   _ Very clear  _ Somewhat clear  _ Not at all clear

3. How helpful to your clinical practice was this article?
   _ Very helpful  _ Somewhat helpful  _ Not at all helpful

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   Participants will be able to:
   Describe the epidemiology and impact on quality of life of trigeminal neuralgia (TN), postherpetic neuralgia (PHN), and painful diabetic nephropathy (PDN)
   _ Achieved  _ Partially achieved  _ Not achieved

   Specify the approach to drug therapy for TN, PHN, and PDN
   _ Achieved  _ Partially achieved  _ Not achieved

   Describe surgical treatments available for TN
   _ Achieved  _ Partially achieved  _ Not achieved

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   ______________________________________________________
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