27. North RB, Kidd DH, Piantadosi S, Carson BS. Percutaneous retrogasserian glycerol rhizotomy: Predictors of success and failure in treatment of trigeminal neuralgia. J Neurosurg 1990;72: 851–856.
28. Saini SS. Retrogasserian anhydrous glycerol injection therapy in trigeminal neuralgia: Observations in 552 patients. J Neurol Neurosurg Psychiatry 1987;50:1536–1538.
29. Constantoyannis C, Kagadis G, Chroni E. Percutaneous balloon compression for trigeminal neuralgias and autonomic cephalalgia. Headache 2008;48:130–134.
30. Skirving DJ, Dan NG. A 20-year review of percutaneous balloon compression of the trigeminal ganglion. J Neurosurg 2001;94:330–332.
31. Kondziolka D, Lunsford LD, Flickinger JC, et al. Stereotactic radiosurgery for trigeminal neuralgia: A multiinstitutional study using the gamma unit. J Neurosurg 1996;84:940-994.
32. Maesawa S, Salame C, Flickinger JC, et al. Clinical outcomes after stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg 2001;94:14–20.
33. Pollock BE, Phuong LK, Gorman DA, et al. Stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg 2002; 97:347–353.
34. Taub E, Munz M, Tasker RR. Chronic electrical stimulation of the gasserian ganglion for the relief of pain in a series of 34 patients. J Neurosurg 1997;86:197–202.

Chapter 36

Postherpetic Neuralgia

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INTRODUCTION

Postherpetic neuralgia (PHN) is one of the most common types of neuropathic pain encountered by practitioners of pain medicine. This syndrome is characterized by prolonged pain after an episode of herpes zoster (HZ), classically known as *shingles*. After the acute rash of HZ has resolved, pain can often persist at the site of the healed rash. This pain, termed *postherpetic neuralgia*, is one the most debilitating features of HZ infection and can persist for months to years after the initial HZ infection. It is well recognized that the incidence of PHN after acute HZ increases with age, occurring in as many as 50% of the population older than 60 years. With the population of individuals 65 and older in industrialized countries increasing rapidly, PHN can be expected to increase in both incidence and prevalence. The associated public health costs, as well as demands placed upon pain practitioners for effective therapies, can be expected to be considerable.

TAXONOMY

Given that PHN occurs after an outbreak of HZ, there has been considerable argument over the precise temporal relationship between PHN and the preceding acute HZ activation. Definitions of PHN vary in terms of both onset and duration of pain, ranging from any pain immediately after the resolution of the HZ rash to pain lasting for 6 months or longer after the rash has healed. Currently, a frequently used clinical case definition is persistent of pain for more than 3 months after resolution of the rash.

EPIDEMIOLOGY

Variable case definitions for PHN have complicated the calculation of PHN incidence and prevalence in the population. It is estimated that more than 1 million people in the United States currently suffer from PHN, with the elderly population disproportionately represented.[1] Both the severity and the duration of PHN increase with age. A study examining the probability of developing PHN after a single episode of HZ reveals that whereas 2% of those younger than 60 years have pain 3 months after acute HZ infection, the odds ratio of continued pain at 12 months increases by 2.33 per 10 years of additional age. Approximately 50% of patients over the age of 70 with PHN have pain lasting over 1 year after resolution of the acute HZ rash. There does not appear to be a gender predilection.

PATHOPHYSIOLOGY

PHN is caused by the varicella-zoster virus (VZV), a double-stranded DNA virus within the herpes family. Viral infection with VZV causes two illnesses: the initial infection, known as *chickenpox*, and a reactivation illness known as *herpes zoster*, or shingles.

During the initial infection with VZV, the virus gains access to and establishes latency within the dorsal root ganglion, the mechanisms of which remain unclear. Owing to cell-mediated immunity acquired during the initial infection with VZV, the virus remains in a latent form. Reactivation is associated with declines in cell-mediated immunity that may result from natural aging, acquired immunodeficiency syndrome (AIDS), organ transplantation, or various other causes of immunocompromised states. During reactivation, the manifestations of HZ occur when the virus replicates in ganglionic nerve cells and migrates along peripheral afferent sensory pathways, causing inflammation and partial denervation of the skin in a dermatomal distribution. Inflammatory changes occur in both the peripheral nerves and the dorsal root ganglia, often lasting months and resulting in demyelination, axonal loss, necrosis, and fibrosis of affected areas. Postmortem studies in patients with PHN pain have found dorsal horn atrophy, demyelination with fibrosis, and cell loss.[2] Current evidence suggests that the combination of demyelinated afferent sensory neurons and dorsal horn neuronal plasticity may result in loss of inhibition and increased activity within small fiber afferents, possibly leading to the pain of PHN.[3,4]

CLINICAL FEATURES

Clinical features of PHN derive from the associated rash and pain of acute HZ (Fig. 36–1 and Box 36–1). HZ initially presents with activation, infection, and spread within the affected sensory ganglion and peripheral afferent nerve. During this period, concurrent inflammation, demyelination, and necrosis may present as a prodrome of pain or discomfort in the corresponding dermatome. This pain can often confuse patients and physicians, masquerading as myocardial infarction, a herniated vertebral disck, or a variety of

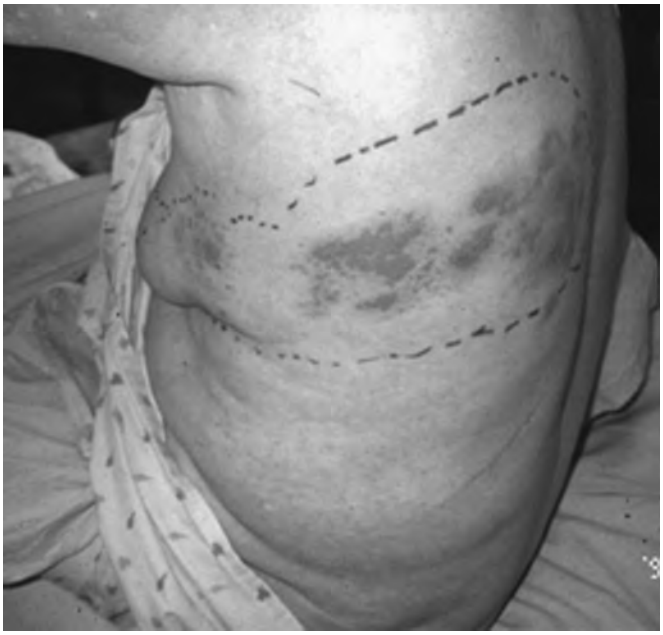

Figure 36–1. A patient displays the thoracic dermatomal rash of herpes zoster (shingles).

gastrointestinal and gynecologic disorders. An important clue to HZ infection during this period is cutaneous hypersensitivity in the affected dermatome.

Once the virus infects the skin, the characteristic rash appears in a classic, red maculopapular eruption that progresses to vesicles in a unilateral dermatomal distribution and, most frequently, involves the T1–L2 and V1 dermatomes. The rash is associated with a painful acute neuritis, described as "burning," "aching," "tingling," "itching," or "stabbing" pain, with severity ranging from mild to severe. The vesicles crust over in 7 to 10 days and the rash heals, sometimes with residual scarring or pigmentation of the affected area (Fig. 36–2).

Continued pain after resolution of the HZ rash classically characterizes PHN, but pain can also occur after an asymptomatic period following the acute HZ infection. Patients with PHN can exhibit a variety of pain and sensory patterns, including constant pain (burning or throbbing), intermittent pain (shooting or stabbing), and allodynia (pain due to a nonpainful stimulus). Areas of hypesthesia and hyperesthesia can also be present in the affected area, sometimes in combination. The development of psychosocial symptoms related to the ongoing pain may include depression, sleep disorders, chronic fatigue, and anxiety.

Box 36–1 Current Diagnosis

- Postherpetic neuralgia (PHN) is a typical form of neuropathic pain, with increased incidence among the older adult population.
- PHN refers to prolonged pain associated with herpes zoster and reflects a reactivation of the original infection with varicella-zoster virus (chickenpox).
- Diagnosis of PHN is based primarily on clinical features.
- PHN case definitions vary but are often defined as pain persisting for greater than 3 mo after resolution of a herpes zoster rash.
- Patients with PHN can exhibit a variety of pain and sensory patterns, including constant pain (burning or throbbing), intermittent pain (shooting or stabbing), and allodynia (pain caused by a nonpainful stimulus). Areas of hypesthesia and hyperesthesia can also be present in the affected area, sometimes in combination.

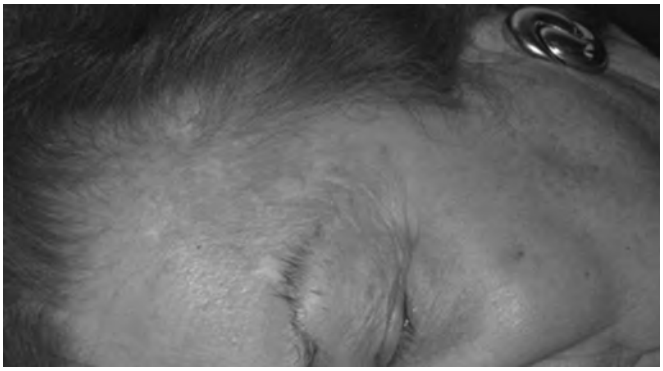

Figure 36–2. Typical hypopigmented scar of postherpetic neuralgia in the V_1 distribution. This patient demonstrated mechanical allodynia and hyperalgesia to pinprick in the affected region extending from her left eyebrow to her scalp.

EVALUATION

Diagnosis of HZ and PHN relies upon a sound history and physical examination, often combined with laboratory diagnostic testing. In a patient with a recent history of dermatomal HZ rash, persistent pain after rash resolution can establish the diagnosis of PHN relatively easily. Examination of the skin may reveal a loss of sensation to touch, temperature, and pinprick in the affected dermatome, often with extension of sensitivity and pain to areas surrounding the rash site. HZ may present without rash, however, and particularly in the elderly ("zoster sine herpete"). Those patients whose HZ infection is characterized by cranial neuritis or meningoencephalitis may also present diagnostic challenges for the physician evaluating a patient with suspected PHN.

In patients who do present with the characteristic zoster rash, the differential diagnosis is primarily between HZ and zosteriform herpes simplex. HZ patients are typically older, whereas herpes simplex patients often experience recurrent episodes and usually do not experience chronic pain.

Although a clinical diagnosis is often sufficient in those patients presenting with the classic HZ rash, for cases involving atypical presentations and possible herpes simplex infection, laboratory testing can be useful. Both immunofluorescence VZV antigen detection and VZV detection by viral polymerase chain reaction (PCR) are excellent tests with high specificity and sensitivity (90%–100%). Serologic testing of acute and convalescent VZV immunoglobulin G (IgG) titers can also be used in establishing a diagnosis of HZ.

MANAGEMENT

Formation of evidence-based guidelines for management of PHN has been complicated by poor study design, including lack of long-term follow-up of study participants, heterogeneous populations, varying PHN case definition among studies, and small sample sizes. In addition, the natural history of PHN is characterized by spontaneous resolution over time; pain reduction may, therefore, mistakenly be attributed to treatment. However, growing collections of rigorous, prospective, randomized, controlled trials show a variety of therapeutic modalities effective in the treatment of PHN[1,5-10] (Box 36–2).

The management of PHN relies primarily upon pharmacotherapy for alleviation of pain symptoms. Even with appropriate management, individual responses to PHN treatments are difficult to predict. With current therapies, up to 40% to 50% of patients with PHN lack satisfactory relief from pain. However, there are several classes of effective medications with favorable side effect

Box 36–2 Current Therapies

- Current management of postherpetic neuralgia (PHN) relies primarily on pharmacologic management of clinical symptoms.
- Classes of medication effective for PHN include tricyclic antidepressants, opioids (both long- and short-acting), anticonvulsants (gabapentin, pregabalin), tramadol, and formulations of topical lidocaine and capsaicin.
- More invasive therapies, such as intrathecal steroids and spinal cord stimulation, have been shown in limited studies to be effective in some patients.
- In general, the practitioner treating PHN should begin with pharmacologic management of PHN, progressing to more invasive therapies only if pain symptoms remain refractory to more conservative management.
- Even with appropriate management, individual responses to PHN treatments are difficult to predict. Even with current therapies, up to 40%–50% of patients with PHN lack satisfactory relief from pain.

profiles that should be considered as first-line agents for the treatment of PHN (Table 36–1). These include tricyclic antidepressants (TCAs), gabapentin (Neurontin), tramadol (Ultram), pregabalin (Lyrica), opioids, capsaicin (Zostrix), and topical lidocaine (lidoderm patch). Various other drug classes and more invasive therapies have been used for treatment of PHN, but these lack strong evidence for first-line treatment. In general, alternative medications or invasive therapies are reserved for those patients lacking response to first-line agents.

TCAs

A significant body of evidence supports the use of TCAs for the treatment of PHN as well as other forms of neuropathic pain. This class of medications operates by inhibiting the reuptake of norepinephrine and serotonin at presynaptic nerve terminals and by enhancing function of the descending antinociceptive pain pathways. The TCAs also possess both anxiolytic and sedative properties that are often useful in the treatment of sleeplessness and anxiety, comorbidities frequently found among sufferers of PHN.

In the clinical management of PHN, both tertiary amines (amitriptyline, doxepin) and secondary amines (nortriptyline, desipramine) are incorporated. Amitriptyline (Elavil) and nortriptyline (Pamelor) are the most frequently used. Both medications are associated with significant decreases in visual analog pain scores of about 50% among randomized, controlled trials of PHN. Whereas the magnitude of benefit appears similar for both amitriptyline and nortriptyline, nortriptyline may be preferred owing to its more favorable side effect profile.

Adverse effects of TCAs include nausea, blurred vision, weight gain, confusion, and dizziness. Tertiary amine TCAs appear to have a more severe side effect profile than secondary amines. Both tertiary and secondary amines possess anticholinergic properties and should be used cautiously in the elderly. Patients often complain of fatigue and dry mouth, with constipation, gait imbalance, falls, urinary retention, and palpitation are also reported. TCAs are also associated with dysrhythmias; therefore, patients with preexisting conduction abnormalities should receive an electrocardiogram before initiating therapy. Relative contraindications to the use of TCAs include recent myocardial infarction, epilepsy, narrow-angle glaucoma, heart block, urinary retention, and concomitant use of monoamine-oxidase inhibitors.

Adverse effects of TCAs are often dose related and can be mitigated by beginning with low doses and titrating slowly. A conservative dosing regimen would begin with 10 mg by mouth at night, gradually increasing by 10 mg per week to an initial target dose of 50 mg at night. If the patient is still experiencing inadequate pain relief, dosage can be increased in 10-mg increments until either adequate pain relief, intolerable side effects, or a maximum dose of 150 mg by mouth occurs. A more aggressive dosing schedule can be employed in healthy and younger patients (<65 yr) and includes beginning at 25 mg by mouth at night, then increasing in 25-mg increments every week until a target dose of 150 mg at night is reached. Once therapy with TCAs is initiated, at least 4 to 8 weeks of treatment is recommended, ideally extended to 3 to 6 months for adequate pain relief.

Anticonvulsants (Gabapentin and Pregabalin)

Gabapentin and pregabalin both act centrally at the $\alpha_2\delta$-subunit of cortical membrane voltage-gated calcium channels and serve to reduce neurotransmitter release. Although exact mechanisms of action are unknown, recent trials have shown that both are effective for reducing pain associated with PHN.[1,6]

Gabapentin, originally developed as adjunctive therapy for refractory epilepsy, has been rigorously evaluated in two recent large, multicenter, placebo-controlled, randomized trials. In both studies, patients on gabapentin, most with dosages from 2400 mg to 3600 mg daily, were found to have a statistically significant reduction in Likert pain score compared with placebo. In one trial, the average decrease in Likert pain scale score was 2.1 on gabapentin versus 0.5 on placebo. Of those patients on gabapentin, the NNT (number of patients needed to treat for one patient to show improvement) was 2.2 for any pain improvement and 2.8 for moderate pain improvement. In a second double-blind, randomized, controlled trial, a 50% or greater decrease in pain as measured by Likert pain scale occurred in 33% of those on gabapentin versus 14% on placebo.

Adverse effects of gabapentin include dizziness, somnolence, and ataxia. It may lead to cognitive impairment as well as gait or balance problems in the elderly. Because gabapentin is excreted renally, dosage adjustment is required in patients with renal insufficiency. In large trials, intolerable adverse effects leading to study withdrawal ranged from 4% to 5% with gabapentin compared with 1.7% with placebo.

Generally, gabapentin has an excellent safety profile and is well tolerated, with side effects frequently resolving within 2 weeks of initiating treatment. Similar to the TCAs, therapy should be initiated at low dosages and with slow titration to prevent adverse effects. A typical dosing regimen would begin with 100 mg three times daily, with 100- to 300-mg dosage increases approximately every 5 to 7 days. Target dosages that have been found beneficial are 900 to 1200 mg daily, with titration as tolerated up to 3600 mg daily in three divided doses. An appropriate gabapentin trial includes a 3- to 8-week titration period to allow for development of tolerance to adverse effects with 1 to 2 additional weeks at the maximum tolerated dose. The U.S. Food and Drug Administration (FDA) has approved gabapentin for use in treating PHN.

Pregabalin, an $\alpha 2\gamma$-ligand at cortical voltage-gated calcium channels has been shown to be effective in reducing pain associated with PHN. Recently approved for treatment of PHN and diabetic neuropathy by the FDA, preabalin has a mechanism of action and side effect profile (dizziness, somnolence, ataxia) similar to those of gabapentin. In a multicenter trial, pregabalin at dosages of 600 mg daily was associated with half of subjects having a 50% or greater reduction in pain compared with 20% on placebo, with a NNT of 3.3. Of note, a greater percentage of patients in this trial discontinued therapy owing to adverse events (32%) than patients in trials of gabapentin. Consequently, clinicians should be cautious with initial dosage and titration schedules when beginning pregabalin treatment.

Dosing of pregabalin should begin at 75 mg twice daily. If the patient tolerates the initial dosage, titration to 150 mg twice daily within 1 week is appropriate. If pain relief is not achieved at

Table 36–1. Useful Medications for Postherpetic Neuralgia

Medication	Initial Dosage	Titration Schedule	Adverse Effects
Tricyclic Antidepressants			
Amitriptyline, nortriptyline	10 mg every evening (older adults) *or* 25 mg every evening	Increase by 10 mg or 25 mg every 7 days to 100 mg, then to maximum of 150 mg nightly if needed	Sedation, xerostomia, confusion, dysrhythmias, weight gain, dizziness
Antiepileptics			
Gabapentin	100 mg 3 times daily	100–300 mg increased every 5 days to total dose of 1800–3600 mg daily	Somnolence, dizziness, fatigue, ataxia
Pregabalin	75 mg twice daily	Increase to 150 mg twice daily within 1 wk	Somnolence, dizziness
Opioids			
Oxycodone sustained release	10 mg every 12 hr	Titrate as needed for pain, balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, hormonal changes
Transdermal fentanyl	12 mcg/hr (older adults) or 25 mcg/hr, changed every 3 days	Titrate as needed for pain, balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, skin irritation, hormonal changes
Morphine (sustained-release)	15 mg every 12 hr	Titrate as needed for pain, balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, hormonal changes
Methadone	2.5 mg (older adults) *or* 5 mg three times daily	Titrate as needed for pain, balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, hormonal changes
Extended-release oxymorphone	5 mg every 12 hr	Titrate as needed for pain, balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, hormonal changes
Transdermal buprenorphine (currently unavailable in the United States)	35 mcg/hr, changed every 3 days	Titrate as needed for pain, balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, skin irritation, hormonal changes
Other Classes of Medications			
Tramadol (immediate-release)	50 mg daily	Increase by 50 mg every 3–4 days to total dose of 100–400 mg daily, in divided doses	Nausea, emesis, dizziness, vertigo, somnolence, headache, constipation
Transdermal 5% lidocaine	One to three patches worn for 12-hr intervals	None	Local skin irritation
5% Lidocaine gel	Apply to affected area	None	Local skin irritation
EMLA	Apply to affected area	None	Local skin irritation
Capsaicin	0.025%–0.075% cream or lotion applied to affected area	None	Localized burning sensation

this dose, practitioners may titrate to 300 mg twice daily, assuming a favorable side effect profile. Several well-designed studies document pain relief within 1 week of initiation of pregabalin. Clinically, a 2-week trial period is suggested to assess for favorable response.

Opioids

Opioids have been used widely in the treatment of both acute and chronic pain, and recent studies support their use for the treatment of PHN. Generally, studies using opioids with follow-up intervals of intermediate length have found benefit in PHN and a direct relationship between dosage and pain reduction. Complications include a greater degree of adverse effects with higher dosages. In addition to trials examining opioid therapy alone for PHN, new studies investigating combination therapy with opioids and gabapentin have also proved effective.[11]

In a recent placebo-controlled, double blind, two-way cross-over study using sustained- release oxycodone (Oxycontin) for treatment of PHN, a 50% decrease in the visual analog score was reported for 22 of the 38 patients who completed the study. The rate of discontinuation owing to treatment failure was similar in both arms (24%), with only 1 patient stopping treatment with controlled-release oxycodone owing to adverse effects.

In the study described previously, opioid therapy was also compared with TCAs and placebo. For instance, using controlled-release morphine sulfate (MS Contin) titrated to a maximum dosage of 240 mg daily, opioid analgesics provided statistically significant improvement in both pain and sleep disturbances. In fact, both opioids and TCAs produced greater pain relief (38% and 32%, respectively) than placebo (11%). Despite greater adverse effects

and more dropouts associated with opioid therapy, comparison of controlled-release morphine and nortriptyline showed greater reductions in PHN pain with morphine.[12] Moreover, subjects who completed all treatment arms preferred opioids to TCAs and placebo.

Buprenorphine (Buprenex) is a partial μ opioid receptor agonist, κ antagonist, and δ antagonist, and initial studies suggest that it may hold value for the treatment of PHN.[13] Recent case studies in patients with neuropathic pain reported pain relief with minimal side effects in patients treated with transdermal buprenorphine in doses of either 35 mcg/hr or 79 mcg/hr. An open-label, long-term follow-up study (>5.7 yr) in 239 cancer and noncancer patients who had participated in a previous double-blind, placebo-controlled transdermal buprenorphine study found that 47.3% experienced satisfactory pain relief, 38.9% reported good pain relief, and 3.8% described complete pain relief from buprenorphine treatment (35 mcg/hr changed every 3 days). Treatment was well tolerated by patients, and minimal side effects were reported. Future randomized, controlled studies with buprenorphine in patients with PHN are needed to further determine its therapeutic role in PHN management.

Combination therapy of opioids with gabapentin has been investigated in a single randomized, double-blind, active-placebo-controlled cross-over study comparing combination treatment with sustained-release morphine/gabapentin and each medication used independently. Patients with PHN and painful diabetic neuropathy were studied. Combination treatment resulted in greater pain relief in both PHN and painful diabetic neuropathy relative to either agent alone or placebo. Benefits of combination therapy extended beyond simple pain reduction to include improvements in daily activities, mood, and health-associated quality of life. Combination therapy was associated with higher incidence of adverse-effects, however. Researchers reported a greater frequency of constipation, sedation, and dry mouth in the combination group compared with groups receiving either gabapentin or morphine alone. Importantly, this study is unique in examining combination therapies for the treatment of PHN. Combination therapy is relatively understudied and merits further investigation as a treatment modality for PHN.

Common side effects of opioid analgesics include constipation, sedation, nausea, and sometimes, hypogonadism. In older adults, cognitive impairment and difficulty with ambulation may occur. Tolerance frequently develops to these adverse effects, although constipation often persists throughout the course of treatment and demands laxative therapy. Caution is suggested in those patients with a history of substance abuse or suicidal ideation because opioid overdose can result in accidental or intentional death and previous history of a substance use disorder elevates the risk of addiction with psychoactive substances. Tolerance to opioids is also frequently seen as a reduction in analgesia over time or even as hyperalgesia (opioid-induced pain sensitivity that leads to a worsening pain state). Despite the development of pharmacologic tolerance, stable dosages can often be achieved in patients responsive to opioid therapy. Finally, patients on opioid analgesics develop physical dependence and should be advised not to abruptly discontinue medication or decrease dosage. Dose adjustments should be determined by a treating clinician in concert with the patient.

There is considerable disagreement over recommended dosing regimens for opioids in the treatment of PHN. As with other classes of medications, initiating low-dose therapy with slow titration to analgesic effects is desirable. This strategy minimizes the potential for adverse medication effects and maximizes the potential for meaningful pain relief and improved function. A recommended course may begin with short-acting opioids at dosage levels that are equianalgesic to 5 to 15 mg of orally administered morphine sulfate every 4 hours as needed. Examples of immediate-release opioid formulations include oxycodone, hydrocodone bitartrate, or propoxyphene combined with acetaminophen, aspirin, or ibuprofen (Tylox/Percocet/Roxicet/Percodan/Cobunox; Lorcet/Lortab/Vicoprofen; Darvocet/Darvon, respectively).

Patients should be monitored for 1 to 2 weeks after initiating therapy with short-acting opioids to determine total daily dosages required for adequate pain control and to monitor for adverse side effects. Further, clinicians must calculate the total daily dose of acetaminophen contained in combination with short-acting opioids. Doses should not exceed 4 g/day in order to avoid hepatic damage.

After 1 to 2 weeks, total daily dosages of short-acting opioids can be converted to long-acting formulations such as sustained-release morphine, sustained-release oxycodone, methadone hydrochloride, transdermal buprenorphine (not available in the United States), extended-release oxymorphone (Opana ER), or transdermal fentanyl (Duragesic). Depending on the clinical situation, access to short-acting opioids for breakthrough pain may be indicated. After conversion to long-acting opioids, an additional 1- to 2-week period of dosage adjustment may be required for optimization. An adequate trial of opioid analgesics may require 4 to 6 weeks of therapy at a stable dosage. With appropriate titration and careful monitoring for adverse effects and functional improvement, dosages can be escalated. The benefit of morphine sulfate equianalgesic dosages exceeding 180 mg daily in the treatment of neuropathic pain have not been investigated with rigorous studies.

Tramadol

Tramadol (Ultram), a centrally acting, weak μ-opioid receptor agonist and reuptake inhibitor of serotonin and norepinephrine, has been shown effective in reducing PHN in a multicenter randomized, controlled clinical trial. In this trial, a greater than 50% reduction in pain was achieved in 78% of those patients on immediate-release tramadol compared with 56% on placebo. Additional studies have suggested that tramadol is effective in reducing PHN pain, particularly in patients experiencing intolerable adverse effects with more potent opioid agonists.

Adverse side effects associated with tramadol include dizziness, constipation, headache, nausea, somnolence, and orthostatic hypotension. These effects are more frequently seen with rapid titration schedules and concomitant use of other medications with similar side effect profiles. Tramadol has been shown to increase seizure risk in patients with a history of seizures or in those patients on other medications that lower the seizure threshold. Owing to tramadol's inhibition of serotonin reuptake, serotonin syndrome (i.e., cognitive changes, neurologic changes, and autonomic instability) may occur if tramadol is used with other serotonergic medications, specifically selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). Dosage adjustment is required in patients with renal and/or hepatic disease.

Suggested starting dosage is 50 mg daily, titrating by 50-mg increments every 3 to 4 days. The maximum dosage of tramadol is 100 mg four times daily, with reduced dosages of 300 mg daily in divided doses in elderly patients. A 4-week trial period is recommended when starting tramadol treatment.

Topical Lidocaine

Lidocaine in the form of a gel, an eutectic mixture of local anesthetics (EMLA = lidocaine 2.5% and prilocaine 2.5%), and lidocaine-impregnated patches appear effective in the treatment of PHN. The lidocaine patch (Lidoderm), consisting of a 10 x 14-cm nonwoven, polyethylene backing and medication-containing adhesive of 5% lidocaine (700 mg/patch), has been approved by the FDA for treatment of PHN. Compared with systemic analgesics, topical therapies offer the ability to reduce the pain

of PHN with little to no systemic side effects. The lidocaine patch can be cut to the desired dimensions based upon cutaneous pain patterns and produces an analgesic effect without associated local anesthesia. Drug absorption is directly related to the area of contact between the skin and the patch as well as the duration of patch application. Assuming normal hepatic function, blood levels of lidocaine are minimal when following a 12-hours on/12-hours off lidocaine patch application schedule.

Three randomized, controlled trials have shown the 5% lidocaine patch to effective for reducing pain and allodynia associated with PHN.[14,15] In one study, a statistically significant decrease in visual analog score was seen in patients receiving 5% lidocaine patch application, with the benefit persisting for longer than 4 hours after removal. This suggests that the pain benefit associated with the lidocaine patch extends beyond the initial analgesia associated with patch application. Additional benefit appears to derive from the protective effect of the patch on allodynic skin, which prevents mechanical irritation and exacerbation of pain symptoms. Accordingly, the lidocaine patch appears most effective in PHN patients who display allodynia without cutaneous sensory loss. Complete pain relief using only the lidocaine patch is rare, but partial relief has been seen in up to 91% of patients in one randomized, controlled trial of the 5% lidocaine patch.

Adverse effects from the lidocaine patch are rare. Patients who discontinue therapy usually report ineffective cutaneous pain reduction or local skin irritation.

Current treatment recommendations (and FDA approval) suggest a 12-hours on/12-hours off application schedule of no more than three 5% lidocaine patches.[16] If EMLA is applied, patients should spread the cream over the affected area once a day and cover it with an occlusive dressing. A 2-week trial period is suggested to assess for benefit before abandoning therapy.

Other Topical Agents (Capsaicin and Topical Aspirin Ointment/Cream)

Capsaicin (Zostrix) is an alkaloid extract derived from hot chili peppers that is available as both a cream and a lotion in strengths of 0.025% and 0.075%. The mechanism of action in humans appears to be through degeneration of intracutaneous nerve fibers, thereby providing pain relief through neurodegenerative changes. Many believe that capsaicin depletes neuronal stores of neurotransmitters like substance P and other neuropeptides. Ultimately, local nociceptive function is inactivated and pain relief ensues.

Two randomized trials have shown capsaicin to be modestly effective in treating PHN.[10] In a 6-week randomized, double blind, placebo-controlled trial of 0.075% capsaicin, a modest reduction in visual analog score (~23% decrease from baseline after 4 wk) was observed in 65% of patients receiving capsaicin treatment. The primary side effect of capsaicin in this study was a burning sensation, reported in 60% of patients on capsaicin versus 30% on placebo. Of those patients on capsaicin after 2 years, 77 of 83 patients maintained pain relief with capsaicin.

Topical aspirin ointment has been examined in randomized, double-blinded studies in combination with 5% lidocaine gel, and a decrease of 73% in the visual analog scale has been reported in patients treated with these agents. Significant methodological problems with the trial, including comparison of two active agents to the baseline pain condition, limit the evaluation of aspirin as an effective treatment for PHN.

Based on initial data, neither capsaicin nor topical aspirin formulations are currently recommended as first-line agents for treatment of PHN. However, given that topical agents are less likely associated with systemic side effects, they may serve as useful adjuncts for pain relief.

Interventional Therapies

Neuraxial Steroids

In general, invasive therapies for PHN are reserved for those patients with pain refractory to more conservative, pharmacotherapy-based treatment strategies. At present, interventional therapies are supported by limited data for efficacy in the treatment of PHN.

Intrathecal steroid administration for PHN has been evaluated in a randomized, double-blind, controlled trial.[17] In this study, patients with refractory PHN failing conventional therapy were randomized to (1) no lumbar puncture; (2) 3 ml of 3% intrathecal lidocaine; or (3) 60 mg of preservative-free methylprednisolone in 3 ml of 3% lidocaine. Results indicated that 90% of patient receiving intrathecal methylprednisolone reported good to excellent pain relief coupled with a reduction in their usage of nonsteroidal anti-inflammatory medications. Analgesia in these patients persisted through 2 years of follow-up with no observed complications related to treatment.

Epidural steroid use in PHN patients has also been studied in a randomized, controlled, single-blinded study comparing intrathecal methylprednisolone injection with epidural methylprednisolone injection administered weekly for 4 weeks. No benefit was observed in the epidural injection group, but significant relief was seen in the intrathecal injection group at both 1 and 24 weeks after study completion.

Whereas intrathecal methylprednisolone injection was associated with no adverse events in the randomized, controlled trial described previously, other studies of intrathecal steroid injection for pain states have documented risks including chemical meningitis, chronic arachnoiditis, and transverse myelitis.[18] Complications such as aseptic and bacterial meningitis, cauda equina syndrome, and cerebral vein thrombosis have also been published in association with intrathecal steroid injection.

Based on limited data involving small patient numbers, intrathecal methylprednisolone appears effective for PHN. Based on the invasiveness of this therapy, along with associated risks of neuraxial steroid injection and the difficulty in obtaining preservative-free methylprednisolone in the United States, clinicians should consider intrathecal steroid injection only in patients with PHN refractory to more conservative medical therapies.

Spinal Cord Stimulation

The application of spinal cord stimulation (SCS) in PHN stems from the search for more effective treatments for this painful disease and from a desire to avoid the disadvantages of systemic pharmacotherapy. SCS of the dorsal columns may activate spinal and supraspinal inhibitory pain processes and reestablish a balance between excitatory and inhibitory pathways in dorsal horn cells. Overall, the literature reveals mixed results in treating PHN with spinal cord stimulation. For instance, Kumar and coworkers,[19] in a prospective case series, showed that three eighths (38%) of PHN patients reported pain relief after implantation, and only one fourth (25%) described pain relief at an average follow up of 7.3 years. However, Harke and associates,[20] in a prospective case series, demonstrated that 23 of 28 patients (82%) with PHN reported long-term pain relief at more than 2 years. Further, patients experienced significant improvements in activities of daily living noted by the pain disability index. More than 50% of these PHN patients no longer required pain medications during SCS treatment. Meglio and colleagues,[21] in a retrospective case series, found that 6 of 10 patients with chronic PHN reported 53% pain relief with SCS over a 46-month follow-up period.

In sum, despite the results of lower-quality evidence to support the use of SCS in PHN, SCS may be of value in treating unbearable PHN pain unresponsive to pharmacologic treatments.

Other Therapies

Numerous other therapies have been attempted to reduce pain associated with PHN including sympathetic blockade, skin excision, dorsal root entry lesions, cordotomy, thalamotomy, SCS, and deep brain stimulation.[22,23] All of these therapies have either lacked efficacy for PHN or involved uncontrolled trials with small numbers of patients. Given the highly invasive nature of these treatments, combined with their associated risks, all other options should be considered before initiating these therapies.

Alternative therapies, such as acupuncture, transcutaneous electrical nerve stimulation, topical benzydamine, geraniuim, and peppermint oil have been described in anecdotal reports to be successful. In patients who fail conventional PHN treatments, these noninvasive therapies may be considered based on individual patient presentation and interest.

CONCLUSION: TREATMENT RECOMMENDATIONS

Treatment of established PHN should begin with less invasive therapies possessing favorable side effect profiles whose efficacy has been established through rigorous research trials. A diagram of suggested treatment strategies is shown in Box 36–2. First-line agents for PHN may include TCAs, the 5% lidocaine patch, pregabalin, and gabapentin. Lidocaine patches have been found effective for treatment of PHN, particularly in patients with a marked allodynic component to their pain. The favorable side effect profile combined with lack of systemic toxicity suggests the lidocaine patch to be safe and effective for a variety of PHN patients.

In conjunction with the 5% lidocaine patch, amitriptyline and nortriptyline along with gabapentin and pregabalin have been found effective in a variety of randomized, controlled trials for PHN. Given the more favorable side effect profile of nortriptyline, clinicians should consider its use over amitriptyline, particularly in older adults. Gabapentin or pregabalin may also be incorporated into therapy alone or in concert with TCAs and transdermal lidocaine. In fact, studies suggest that antiepileptic medications may be better tolerated than TCAs.

In patients who fail to respond to these agents, initiating a short-acting opioid followed by conversion to long-acting forms in 1 to 2 weeks is supported by current evidence as effective therapy. Opioids may be considered after other agents have failed to provide reasonable analgesia. Clinicians should monitor patients for adverse effects, tolerance, physical dependence, and addiction.

In patients with PHN refractory to pharmacotherapeutic management, the clinician may consider other less well supported therapies such as SCS, capsaicin, topical aspirin, or intrathecal methylprednisolone. Given the lack of good evidence for these treatments and associated risks of neuraxial steroid injection, these therapies should be reserved for patients refractory to more conventional and less invasive PHN treatments.

Unfortunately, data on therapy for PHN show that as many as 40% to 50% of patients will experience unsatisfactory pain control. In these patients, treatment may assume a trial-and-error type pattern, although a reasonable approach focuses on modalities that appear safe and reasonable. Fortunately, even patients with refractory PHN appear to improve over time; that is, almost 50% of patients do report improvement in PHN symptoms. It is expected that continued research into the mechanisms and treatment of PHN will define more effective therapeutic options, whereas preventive strategies and early treatment of acute herpes zoster will reduce the incidence of PHN in the general population.

REFERENCES

1. Johnson RW, Dworkin RH. Treatment of herpes zoster and postherpetic neuralgia. BMJ 2003;326:748–750.
2. Watson CP, Watt VR, Chipman M, et al. The progrosis with postherpetic neuralgia. Pain 1991;46:195–199.
3. Oaklander AL. The density of remaining nerve endings in human skin with and without postherpetic neuralgia after shingles. Pain 2001;92:139–145.
4. Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. Clin J Pain 2000;16(2 Suppl.):S12–S20.
5. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:2271–2284.
6. Freynhagen R, Strojek K, Griesing T, et al. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomized, double-blind, multicentre, placebo-controlled trial of flexible and fixed dose regimens. Pain 2005;115:254–263.
7. Hempenstall K, Nurmikko TJ, Johnson RW, et al. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med 2005;2:e164.
8. Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in postherpetic neuralgia: a randomized, double blind, placebo-controlled trial. Pain 2003;103:323–331.
9. Meier T, Wagner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of total peripheral neuropathic pain syndromes: a randomized, double blind, placebo-controlled study. Pain 2003;106:151–158.
10. Bernstein JE, Korman NJ, Bickers DR, et al. Topical capsaicin treatment of chronic postherpetic neuralgia. J Am Acad Dermatol 1989;21:265–270.
11. Gilron I, Baily J, et al. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005;352:1324–1334.
12. Raja SN, Haythornthwaite JA, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2002;59:1015–1021.
13. Lee K, Akil H, Woods JH, et al. Differential bending properties of oripavines at cloned mu and delta opioid receptors. Eur J Pharmacol 1999;378:323–330.
14. Rowbotham MC, Davies PS, Verkempinck C, et al. Lidocaine patch: double-blind controlled study of a new treatment method for postherpetic neuralgia. Pain 1996;65:39–44.
15. Galer BS, Jehsen MP, Ma T, et al. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double blind, vehicle-controlled, 3-week efficacy study with use of Neuropathic Pain Scale. Clin J Pain 2002;18:297–301.
16. Endo Pharmaceuticals Inc: Lidoderm (lidocaine patch 5%) prescribing information. Chadds Ford, PA: Endo Pharmaceuticals Inc, 2000.
17. Kotani N, Kushikata T, Hashimoto H, et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. N Engl J Med 2000;343:1514–1519.
18. Nelson DA. Intraspiral therapy using methylprednisolone acetate: twenty-three years of clinical controversy. Spine 1993;18:278–286.
19. Kumar K, Toth C, et al. Spinal cord stimulation for chronic pain in peripheral neuropathy. Surg Neurol 1996;46:363–369.
20. Harke H, Gretenkort P, et al. Spinal cord stimulation in postherpetic neuralgia and in acute herpes zoster pain. Anesth Analg 2002;94:694–700.
21. Meglio M, Cioni B, et al. Spinal cord stimulation (SCS) in the treatment of postherpetic pain. Acta Neurochir Suppl (Wien) 1989;46:65–66.
22. Douglas MW, Johnson RW, Cunningham AL, et al. Tolerability of treatments for postherpetic neuralgia. Drug Saf 2004;24:1217–1233.
23. Loeser J. Surgery for postherpetic neuralgia. In Watson CP (ed): Herpes Zoster and Postherpetic Neuralgia. Amsterdam: Elsevier, 1993; pp 221–237.