CHAPTER 51

Herpes Zoster and Postherpetic Neuralgia

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The objective of this chapter is to provide an overview of the epidemiology, natural history, pathophysiology, treatment, and prevention of herpes zoster and postherpetic neuralgia. Herpes zoster ("shingles") is a viral infection that is accompanied by acute pain in the majority of patients. The pain associated with herpes zoster does not resolve in a substantial number of patients, and postherpetic neuralgia (PHN) is diagnosed when herpes zoster pain persists. The results of research on PHN—a chronic peripheral neuropathic pain condition—have added greatly to knowledge of the pathophysiology and treatment of neuropathic pain.

HERPES ZOSTER

EPIDEMIOLOGY OF HERPES ZOSTER

Following a primary chicken pox infection, the varicella-zoster virus (VZV) establishes latency in sensory ganglia throughout the nervous system. Herpes zoster (shingles) is the reactivation of the virus and its spread from a single dorsal root or cranial nerve ganglion to the corresponding dermatome and neural tissue of the same segment.[1,2] Herpes zoster has the highest incidence of all neurologic diseases, occurring annually in approximately 1 million people in the United States, during the lifetimes of as much as 20% to 30% of the population, and in as many as 50% of those living until age 85.[1,3–6] The likelihood of recurrent zoster, however, is reported to be 5% or less,[1,5,7] and the true incidence may even be lower because a portion of these cases may have been zosteriform, recurrent herpes simplex infections.

A fundamental epidemiologic feature of zoster is a marked increase in incidence with aging. For example, the incidence of herpes zoster per 1000 person-years in a recent U.S. retrospective database study was 2.1 for persons aged 40 to 49 years, 4.2 for 50 to 59, 6.0 for 60 to 69, 8.6 for 70 to 79, and 10.7 for 80 and older.[7] In the placebo group in the zoster vaccine trial known as the Shingles Prevention Study (which was prospective, used active surveillance in a community-based population, and used PCR for definitive diagnosis of herpes zoster cases), the incidence of herpes zoster was 11.8 cases per 1000 persons per year in adults aged 60 and older.[8]

The incidence of herpes zoster is also significantly increased in patients with suppressed cell-mediated immunity—including HIV, AIDS, certain cancers, organ transplants (especially bone marrow transplant), immune-mediated diseases, and immunosuppressive treatments—compared to immunocompetent individuals.

Zoster epidemiology is ultimately determined by the transmission and spread of VZV in populations. The most important condition in the spread of VZV is the primary chicken pox infection, but latent and reactivated VZV infections also play important roles in maintaining VZV infection in populations.[9] Latently infected elderly adults and immunosuppressed patients are important reservoirs of virus because VZV is more likely to reactivate in these groups. When zoster occurs, VZV can be transmitted during the vesicular phase of the rash and cause primary infection when there is contact with a seronegative individual. A zoster exposure with a seropositive, latently infected individual may result in a subclinical reinfection and boost of humoral and cellular VZV immunity, but it is unlikely to cause varicella or herpes zoster.[9]

NATURAL HISTORY OF HERPES ZOSTER

The presentation of pain in herpes zoster is variable. In the majority of patients, a prodrome of dermatomal pain precedes the appearance of the characteristic unilateral rash.[10–12] This prodrome begins several days before rash onset in almost all cases, but a series of patients with prodromal pain preceding the appearance of the rash by 7 to more than 100 days has been reported.[13] Thoracic dermatomes are the most commonly affected sites in herpes zoster and account for 50% to 70% of all cases; cranial (especially the ophthalmic division of the trigeminal nerve), cervical, and lumbar dermatomes each account for 10% to 20% of cases, and sacral dermatomes are affected in 2% to 8% of cases.[14] The rash becomes vesicular after several days, then forms a crust, and loss of all scabs usually occurs within 2 to 4 weeks.

Pain in the affected dermatome accompanies the rash in most patients. Those who did not have a painful prodrome typically begin to experience pain at rash onset or shortly afterwards (Fig. 51-1). This acute herpes zoster pain gradually resolves before or shortly after rash healing in most cases. Severe acute pain in herpes zoster interferes with patients' abilities to carry out normal activities of daily living and, not surprisingly, is associated with greater use of analgesic medications.[15,16]

Dermatomal pain without a rash, referred to as *zoster sine herpete*, has also been described, and the finding of VZV DNA in the cerebrospinal fluid of patients with prolonged radicular pain and no rash provides evidence of this syndrome.[17]

In addition to acute pain, the morbidity of herpes zoster includes neurologic disorders and ophthalmologic, cutaneous, and visceral complications. The types of neurologic complications include motor neuropathy, cranial polyneuritis, transverse myelitis, meningoencephalitis, and cerebral angiitis and stroke after ophthalmic zoster.[7,16] Ophthalmologic complications have been described in 2% to 6% of zoster cases, including keratitis, uveitis, iridocyclitis, panophthalmitis, and glaucoma.[18] Elderly and especially immunosuppressed patients are at greater risk for most of the complications of herpes zoster.

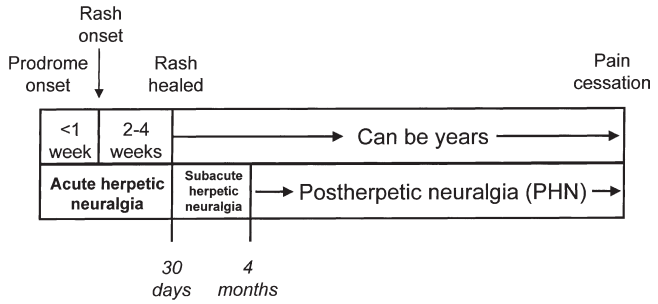

FIGURE 51-1 Timeline of pain experienced by herpes zoster patients.

TREATMENT OF HERPES ZOSTER

The main goals of the treatment of herpes zoster are to relieve acute pain and prevent postherpetic neuralgia. Treatment of herpes zoster patients with the antiviral agents acyclovir, famciclovir, valacyclovir, and brivudin (the latter only available in some European countries) inhibits viral replication and has been shown to reduce the duration of viral shedding, hasten rash healing, and decrease the severity and duration of acute pain.[2,19] The results of randomized controlled trials and meta-analyses are conflicting as to whether antiviral agents prevent PHN, partly because of heterogeneity in definitions of PHN and study design, although the duration of pain is decreased in some of these trials.[2,19–21] Therefore, based on reduction in acute pain and the potential for reduction in pain duration, antiviral therapy is recommended as first-line treatment in herpes zoster patients who are aged 50 years and older, have moderate or severe rash, have moderate or severe pain, have ophthalmic involvement, or are immunocompromised.[2,22] Famciclovir, valacyclovir and brivudin offer more convenient dosing and higher and more reliable blood levels of antiviral activity compared to acyclovir.

Some patients will not have their acute pain adequately controlled with antiviral therapy and simple analgesics. Approximately 20% of patients over age 50 continue to have pain 6 months after their rash despite antiviral treatment beginning within 72 hr of rash onset.[20] How then can acute pain and the risk of chronic pain be further reduced, beyond that currently achieved by antiviral therapy? Corticosteroids, opioids, gabapentin, tricyclic antidepressants, and neural blockade have been investigated or considered as strategies to achieve these goals.[22]

Randomized controlled clinical trials (RCTs) demonstrated that the addition of a corticosteroid reduced acute pain but did not contribute significantly beyond the benefits achieved by antiviral therapy alone in reducing prolonged pain.[23,24] The evidence from these trials indicated that corticosteroids do not prevent PHN.

A randomized controlled trial of oxycodone, gabapentin, or placebo in older adults with herpes zoster showed that oxycodone but not gabapentin provided significantly greater pain relief than placebo.[25] This trial was not powered to analyze PHN, and there are no other controlled trials of the effect of opioids or gabapentin on PHN when used during the acute phase of herpes zoster, except for a crossover study that showed greater pain relief with a single dose of 900 mg of gabapentin versus placebo.[26]

A placebo-controlled trial of amitriptyline 25 mg once daily for 3 months beginning within 48 hr of rash onset, and a reanalysis examining the subgroup of patients also treated with an antiviral, suggested that amitriptyline reduced the prevalence of PHN at 6 months.[27,28] However, amitriptyline is associated with a high rate of adverse events in older adults and this study is in need of replication. No trials have examined the effect of tricyclic antidepressants on acute pain in herpes zoster.

Regarding neural blockade, the results of a randomized controlled trial in patients with herpes zoster treated with oral antiviral therapy showed that a single epidural injection of steroids and local anesthetics relieved acute pain within the first month after rash onset significantly better than usual care but did not reduce the risk of developing PHN.[29] RCTs of multiple epidural injections, continuous epidural infusions, or repetitive paravertebral injections of anesthetics and steroids during herpes zoster reduced PHN or time to complete cessation of pain.[30–33] Although treatment of herpes zoster patients with multiple epidural injections or continuous epidural infusions is unlikely to be feasible in most settings, these data suggest that aggressive analgesia can be effective in patients with herpes zoster and ongoing moderate to severe pain.

Even if the risk of developing PHN is not reduced by combining antiviral therapy with analgesic or corticosteroid treatment in patients with herpes zoster, effective relief of acute pain is a critical treatment goal. For patients with moderate to severe pain, treatment with a strong opioid analgesic (e.g., oxycodone) is recommended in combination with antiviral therapy. If moderate to severe pain in patients with herpes zoster has not responded rapidly to treatment with an opioid analgesic and antiviral therapy, then the addition of a corticosteroid can be considered. For patients with pain that is inadequately controlled by antiviral agents in combination with oral analgesic medications and/or corticosteroids, referral to a pain specialist or pain center is recommended to evaluate eligibility for neural blockade.[22]

PREVENTION OF HERPES ZOSTER

A live attenuated zoster vaccine induces significant increases in the cellular immune response to VZV in older adults. Given that cellular immunity to VZV declines with age, the Shingles Prevention Study addressed the questions as to whether vaccination against VZV would decrease the incidence and/or severity of herpes zoster and PHN among older adults.[8]

The study was a randomized, double-blind, placebo controlled trial in 38,546 community-dwelling persons aged 60 and older. Subjects were followed for a median of 3 years. A total of 957 confirmed cases of herpes zoster (315 among vaccine recipients and 642 among placebo recipients) and 107 cases of PHN (27 among vaccine recipients and 80 among placebo recipients) were included in the efficacy analysis. The zoster vaccine reduced the burden of illness (a pain severity by duration measure) due to herpes zoster by 61.1% ($p < 0.001$), reduced the incidence of PHN by 66.5% ($p < 0.001$), and reduced the incidence of herpes zoster by 51.3% ($p < 0.001$). Reactions at the injection site were more frequent among vaccine recipients but

were generally mild. Based on these findings, the U.S. Food and Drug Administration (FDA) licensed the zoster vaccine for the prevention of herpes zoster in immunocompetent adults aged 60 and older in 2006. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) unanimously recommended the vaccine for the prevention of herpes zoster in immunocompetent adults aged 60 and older and added the vaccine to the U.S. routine adult immunization schedule.[34] The effect that the zoster vaccine will have on the pain of herpes zoster and PHN will depend on the extent of vaccine uptake in the population and the durability of vaccine response, both of which are currently under investigation.

POSTHERPETIC NEURALGIA

EPIDEMIOLOGY AND NATURAL HISTORY

A variety of definitions of PHN have been used by clinicians and investigators, ranging from any pain persisting after rash healing to pain that has persisted at least 6 months after rash onset.[35] The results of recent studies, however, suggest that the pain associated with herpes zoster has three phases—an acute herpetic neuralgia that accompanies the rash and lasts for approximately 30 days after rash onset, a subacute herpetic neuralgia that lasts from 30 to 120 days after rash onset, and PHN, defined as pain that persists for at least 120 days after rash onset (see Fig. 51-1).[36–38] Although this provides a validated definition for research on PHN, it is probably unnecessary to distinguish between subacute herpetic neuralgia and PHN when treating patients with pain persisting after rash healing.

Because the proportion of herpes zoster patients with pain declines with time, estimates of the percentage of patients who develop PHN depend on its definition. In different clinic and community studies, 9% to 34% of adult zoster patients were reported to develop PHN defined variously as pain persisting after rash healing or for at least several months after rash onset.[2,7,35] There have been no systematic attempts to investigate the prevalence of PHN, and estimates of the number of cases have ranged from 500,000 to 1 million in the United States.[39]

PHN is a chronic pain syndrome that can last for years and cause substantial suffering and reduction in quality of life. As is true of other chronic pain syndromes, patients develop depression and other types of psychological distress as well as physical, occupational, and social disability as a consequence of their unremitting pain.[40–42]

There is evidence that pain in PHN can be discontinuous, with pain-free intervals of varying durations occurring.[43] Indeed, PHN can develop even in herpes zoster patients who have not had acute pain.[44]

The quality of pain in PHN compared to herpes zoster has been examined in several studies.[45–47] Sharp, stabbing pain was found to be more common in patients with zoster than in patients with PHN, whereas burning pain was more common in PHN patients and much less likely to be reported by patients with zoster. The investigators noted that the word *tender* was chosen by both groups of patients to describe allodynia (i.e., pain in response to a stimulus that does not normally provoke pain). These adjectives reflect the three different types of pain that have been distinguished in research on PHN—a steady throbbing or burning pain, an intermittent sharp or shooting pain, and allodynia.

There are a considerable number of recent studies in which risk factors for PHN have been investigated. Older age is the most well-established risk factor for PHN.[3,7] For example, as early as 50 years ago it was reported that persisting pain was infrequent in herpes zoster patients under 40 years of age, but that the proportion of patients with pain lasting 1 year or more approached 50% in those over age 70.[48] Many independent studies have reported that patients with more severe acute pain are at greater risk for PHN.[38,49] As noted above, the majority of herpes zoster patients have a painful prodrome before their rash appears, and several studies have found that these patients have a greater risk of PHN than patients who did not have a prodrome.[38,49] Greater severity and duration of the herpes zoster rash are additional risk factors for the development of PHN that have been identified in multiple studies.[38,49]

PATHOPHYSIOLOGY

Except for age and psychosocial factors, the risk factors for PHN that have been identified can all be considered concomitants of a more severe infection. More severe zoster infections are accompanied by greater neural damage, and it has been proposed that this neural damage contributes prominently to the development of PHN.[50] But the nature of this damage and the specific mechanisms by which it causes the persisting pain of PHN remain unclear. What limited knowledge there is of the pathophysiology of PHN derives from studies of neuropathology, sensory dysfunction, and pharmacologic response. At the present time, there is considerable agreement that different peripheral and central mechanisms contribute to PHN, and that the qualitatively different types of pain that characterize PHN probably have different underlying mechanisms. This suggests that there may be pathophysiologically distinct subgroups of patients with PHN or that more than one mechanism may be involved in individual patients or both.[51,52]

Watson and his colleagues[53] have conducted an elegant series of postmortem studies of patients of who were suffering from PHN at the time of death and of patients with a history of herpes zoster whose pain did not persist beyond rash healing. In these studies, dorsal horn atrophy and pathologic changes in the sensory ganglion were found on the affected side (and not on the unaffected side) in patients with PHN, but not in patients with a history of herpes zoster whose pain did not persist. In a more recent set of studies using punch skin biopsy, reductions in epidermal nerve fiber density were found in the affected dermatome but not on the contralateral unaffected side in patients with PHN.[54,55] Notably, in both the postmortem studies and the punch-skin biopsy studies, the the pathologic features were characteristic of only the affected side in patients with PHN and were not found in patients with a history of zoster whose pain did not persist.

Rowbotham, Fields, and Petersen[51,52,56,57] have conducted an important series of studies of sensory dysfunction and pharmacologic response that address the pathophysiology

of PHN. PHN patients with prominent allodynia were found to have relatively normal sensory function as assessed by thermal thresholds and were also more likely to report pain relief following local anesthetic infiltration with lidocaine than patients with primarily constant pain. These authors conclude that at least two different mechanisms may contribute to PHN, and propose that the mechanism of allodynia in PHN is abnormal activity in preserved primary afferent nociceptors that have been damaged by the varicella-zoster virus but that remain in continuity with their central targets. Activity in these "irritable" nociceptors may initiate and then maintain a state of central sensitization in which input from large fiber afferents that respond to nonpainful mechanical stimuli causes allodynia.

As opposed to patients with prominent allodynia, PHN patients with predominantly continuous pain were found to have sensory loss in the areas where they have the most pain. This suggests that continuous pain in PHN is caused by a different mechanism than allodynia, possibly involving central structural and functional changes accompanying deafferentation. These may include a structural reorganization of the spinal cord that involves abnormal synaptic connections, as well as functional abnormalities resulting from deafferentation involving hyperexcitability of dorsal horn neurons.

TREATMENT

Since publication of the first randomized controlled trials in the early 1980s, tricyclic antidepressants (TCAs) have been considered a first-line treatment for patients with PHN.[58] The efficacy of gabapentin, high-concentration capsaicin patch, lidocaine patch 5%, opioid analgesics, pregabalin, and tramadol, has now also been demonstrated by the results of RCTs in patients with PHN. These medications provide an evidence-based approach for the treatment of PHN.[59–65]

The initial choice of these medications should be guided by the adverse event profiles, potential for drug interactions, and patient comorbidities and treatment preferences, especially because there are no replicated data demonstrating superior effectiveness of one drug over another. In general, gabapentin, high-concentration capsaicin, lidocaine patch 5%, and pregabalin can be considered first-line treatments for PHN, whereas opioid analgesics, tramadol and TCAs are more typically second-line treatments because they generally require greater caution in the often elderly patient with PHN.[66]

Gabapentin. Patients with PHN have been treated with anticonvulsant medications for many years. Gabapentin, a second-generation antiepileptic drug, was associated with a statistically significant reduction in daily pain ratings as well as improvements in sleep, mood, and quality of life at daily dosages of 1800 to 3600 mg in two large clinical trials.[67,68] Side effects of gabapentin include somnolence, dizziness, and (less often) mild peripheral edema, which requires monitoring and possibly dosage adjustment but usually not treatment discontinuation. Gabapentin may cause or exacerbate gait and balance problems and cognitive impairment in the elderly. Dosage adjustment is necessary in patients with renal insufficiency, but its generally excellent tolerability, safety, and lack of drug interactions distinguish gabapentin from the other oral medications used in the treatment of PHN.

To reduce side effects and increase patient compliance with treatment, gabapentin should be initiated at low dosages—100 to 300 mg in a single dose at bedtime or 100 mg 3 times daily—and then titrated by 100 mg 3 times daily as tolerated. Because of variability in gabapentin absorption, the final dosage should be determined either by complete pain relief, which is rare, or by unacceptable side effects that do not resolve over a few weeks.

High-concentration capsaicin patch. The results of two RCTs in patients with PHN showed that a single application of a high-concentration patch versus a low-concentration control patch was efficacious in reducing pain from the second week after the capsaicin application throughout a subsequent 8-week period; this effect was also observed over 12 weeks in secondary analyses.[68,69] Application of the high-concentration capsaicin patch in patients with PHN was safe and well tolerated, and adverse events were limited to transient increases in pain associated with patch application and application-site reactions (e.g., erythema).

Because a single treatment application may be associated with sustained reductions in pain that last for 2 to 3 months, the high-concentration capsaicin patch has the potential to provide a novel addition to existing treatments for PHN, which are typically administered 1 or more times each day. However, the long-term benefits of the high-concentration capsaicin patch are unknown, and the safety and efficacy of repeated applications must be evaluated.

Lidocaine patch 5%. There are two published, double-blind, vehicle-controlled, randomized trials of lidocaine patch 5% in PHN.[70,71] In these studies, PHN patients with allodynia obtained statistically significantly greater pain relief with lidocaine patch 5% compared with vehicle-control patches containing no lidocaine. Lidocaine patch 5% is a topical preparation that has excellent safety and tolerability, and the only side effects involve mild skin reactions (e.g., erythema, rash). Systemic absorption is minimal but must be considered in patients receiving oral Class I antiarrythmic drugs such as mexiletine.

Treatment with the lidocaine patch 5% consists of the application of a maximum of three patches daily for a maximum of 12 hr applied directly to the area of maximal PHN pain and allodynia, which typically overlaps the affected dermatome. The lidocaine patch 5% is not approved for patients with herpes zoster, and it should not be used in patients with open lesions because the available formulation is not sterile. Importantly, whether the patient obtains satisfactory relief from lidocaine patch 5% will usually be apparent within 2 to 3 weeks and time-consuming dose escalation is not required.

Opioid analgesics. The efficacy of opioid analgesics in patients with PHN was first demonstrated in a double-blind study comparing intravenous morphine with placebo.[72] By providing evidence that PHN pain could be temporarily relieved by infusions of opioid analgesics, the results of this study suggested that longer-term oral treatment might also be efficacious. In two double-blind, placebo-controlled, randomized trials of oral opioid analgesics in PHN, controlled-release oxycodone titrated to a maximum dosage of 60 mg daily provided statistically

significant benefits on pain, disability, and allodynia[73] and controlled-release morphine titrated to a maximum dosage of 240 mg daily provided statistically significant benefits on pain and sleep but not on physical functioning and mood.[74]

The most common side effects of opioid analgesics are constipation, sedation, and nausea, as well as cognitive impairment and problems with mobility can occur in elderly patients. Opioid analgesics must be used very cautiously in patients with a history of substance abuse or suicide attempts, and accidental death or suicide can occur with overdose. Patients treated with opioid analgesics may develop analgesic tolerance (i.e., a reduction in analgesic benefit over time), although a stable dosage can often be achieved. All patients will develop physical dependence (i.e., withdrawal symptoms develop with abrupt discontinuation or rapid dose reduction), and must be advised that they should not abruptly discontinue their medication. The risk that substance abuse will develop in patients who do not have a history of substance abuse is not known but thought to be low in the generally elderly patient with PHN.

There are numerous short- and long-acting opioid analgesics available, and treatment can begin with a short-acting medication at morphine oral equianalgesic dosages of 5 to 15 mg every 4 hr as needed. After 1 to 2 weeks of treatment, the total daily dosage can be converted to an equianalgesic dosage of one of the available long-acting opioid analgesics (i.e., controlled-release morphine, controlled-release oxycodone, transdermal fentanyl, levorphanol, and methadone) while the patient continues taking the short-acting medication on an as needed basis. With careful titration and monitoring, there is no maximum dosage of opioid analgesics, but evaluation by a pain specialist may be considered when morphine equianalgesic dosages exceeding 120 mg daily are contemplated.

Pregabalin. Pregabalin is similar in structure to gabapentin and has demonstrated efficacy in RTCs of PHN.[75–77] In a multicenter trial of 173 PHN patients, pregabalin-treated patients had greater decreases in pain than patients treated with placebo (endpoint mean scores 3.60 vs. 5.29, $p = 0.0001$).[75] The proportions of patients with greater than 50% decreases in mean pain scores were greater in the pregabalin than in the placebo group (50% vs. 20%, $p = 0.001$). Dizziness, somnolence, peripheral edema, amblyopia, dry mouth and gait disturbances were the most common adverse effects of the medication.

Pregabalin should be initiated at 150 mg/day in two or three divided doses. Frail older patients may require lower starting doses. The dose may be increased to 300 mg/day in two or three divided doses within 1 week depending on clinical response and any adverse effects. The maximum dose of 600 mg/day in two or three divided doses can be considered if the patient does not have adequate pain relief at the risk of significantly higher frequency of adverse effects.

Tramadol. Tramadol is a norepinephrine and serotonin reuptake inhibitor with a major metabolite that is a *mu* opioid agonist. There is one published, double-blind, placebo-controlled, randomized clinical trial of tramadol in PHN,[78] and its results are consistent with studies of other chronic neuropathic pain syndromes.[59] Tramadol was titrated to a maximum dosage of 400 mg daily, and significantly relieved pain and reduced use of rescue medication compared to placebo. The side effects of tramadol include dizziness, nausea, constipation, somnolence, and orthostatic hypotension. These occur more frequently when the dosage is escalated rapidly and with concurrent administration of other drugs with similar side effect profiles. There is an increased risk of seizures in patients treated with tramadol who have a history of seizures or who are also receiving antidepressants, opioids, or other drugs that can reduce the seizure threshold. Serotonin syndrome may occur if tramadol is used concurrently with other serotonergic medications, especially selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors. Tramadol may cause or exacerbate cognitive impairment in the elderly, and dosage adjustment is necessary in patients with renal or hepatic disease. Abuse of tramadol is thought to be rare but has been observed.

To decrease the likelihood of side effects, tramadol should be initiated at low dosages—50 mg once or twice daily—and then titrated every 3 to 7 days by 50 to 100 mg/day in divided doses as tolerated. The maximum dosage of tramadol is 100 mg 4 times daily; in patients aged over 75, the maximum dosage of tramadol is 300 mg daily in divided doses.

Tricyclic antidepressants. An apt summary of studies of the efficacy of TCAs is provided by the title of an article summarizing the relevant literature, "Thirteen consecutive well-designed randomized trials show that antidepressants reduce pain in diabetic neuropathy and postherpetic neuralgia."[58] A recent meta-analysis concluded that TCAs significantly reduce pain in patients with PHN.[79] Amitriptyline is clinically the most widely used TCA in PHN because it is the TCA that has been most extensively studied in PHN and other neuropathic pain syndromes. However, amitriptyline is poorly tolerated and contraindicated in elderly patients.[80,81] In one of the few randomized, double-blind trials that have compared two different treatments in PHN patients, nortriptyline demonstrated equivalent efficacy to amitriptyline but was better tolerated.[82] Based on the results of this study, nortriptyline should now be considered the preferred TCA for the treatment of PHN; desipramine may be used in patients who experience excessive sedation with nortriptyline.

Despite the efficacy of TCAs in the treatment of PHN, their cardiac toxicity[83] and side effect profile require considerable caution when treating older patients with PHN. Dry mouth is the most common side effect, and constipation, sweating, dizziness, disturbed vision, and drowsiness also occur frequently. All TCAs must be used very cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention, and autonomic neuropathy, and a screening EKG to check for cardiac conduction abnormalities is recommended before beginning TCA treatment, especially in patients over 40 years of age. TCAs must be used cautiously when there is a risk of suicide or accidental death from overdose, and TCAs may cause balance problems and cognitive impairment in the elderly. TCAs can block the effects of certain antihypertensive drugs and interact with drugs metabolized by P450 2D6 (e.g., cimetidine, Type 1C antiarrythmics). Because all SSRIs inhibit P450 D26, caution is necessary in the concomitant administration of TCAs and SSRIs to prevent toxic TCA plasma concentrations.

To decrease side effects, all TCAs should be initiated at low dosages—10 to 25 mg in a single dose at bedtime—and should then be slowly titrated as tolerated. It is often claimed that the analgesic effect of TCAs occurs at lower dosages than their antidepressant effect, but there is no controlled evidence of this. Consequently, TCAs should be titrated to dosages of at least 75 to 150 mg daily. For titration above 100 to 150 mg daily, blood levels and the EKG should be monitored. Irrespective of the TCA chosen, it is imperative that patients understand the rationale for treatment, specifically, that TCAs have an analgesic effect that has been demonstrated to be independent of their antidepressant effect. It is important to point out that there are no published randomized clinical trials of either selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine) or selective serotonin and norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine) in PHN and so it is unknown whether these classes of antidepressant medications are efficacious in PHN.

Sequential and combination pharmacologic treatment. There have been few clinical trials in which medications have been directly compared with one another in patients with PHN.[74,82,84,85] Such comparisons would not only make it possible to directly determine whether treatments vary in their efficacy, safety, and tolerability, but when conducted in the same patients, would also make it possible to evaluate the extent to which treatment response to one medication predicts response to another. For example, treatment responses to opioid analgesics and TCAs were uncorrelated in a recent three-period, placebo-controlled crossover trial, which suggests that when patients have not responded to one of these types of medication, they may still respond to the other.[74]

The prescription of combination pharmacotherapy for PHN is common in clinical practice. The efficacy of this practice has been the subject of recent studies of additive or synergistic benefits of combination treatment. In a 5-week double-blind crossover trial, patients with diabetic polyneuropathy or postherpetic neuralgia were randomized to daily active placebo (lorazepam), sustained-release morphine, gabapentin, and a combination of gabapentin and morphine.[84] Baseline mean daily pain (0–10) was 5.72. At maximum tolerated dose, pain was rated at 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine, and 3.06 with the gabapentin–morphine combination ($p < 0.05$ for the combination vs. placebo, gabapentin, and morphine). Results for PHN alone were not reported. Constipation, sedation, and dry mouth were the most common adverse effects. In a 6-week double-blind crossover trial, patients with diabetic polyneuropathy or postherpetic neuralgia were randomized to receive one of three sequences of daily oral gabapentin, nortriptyline, and their combination. Baseline mean pain intensity was 5.4 (0–10 scale). For patients with postherpetic neuralgia, pain with combination treatment (mean 2.5, confidence interval [CI] = 1.4–3.6) was lower than with nortriptyline (mean 2.9, CI = 1.7–4.0) or gabapentin alone (mean 3.4, CI = 2.2–4.5), but the overall effect of drug treatment was not significant ($p = 0.054$), possibly because of small sample size.[85] The most common adverse event was dry mouth secondary to nortriptyline. These results suggest that combination therapy may provide additional pain relief in some individuals with PHN who have responded to one or another agent. Disadvantages of combination therapy include an increased risk of adverse effects as the number of medications is increased.

Beyond first- and second-line treatment. A considerable percentage of PHN patients will not respond to medications when used alone and in combination. For these patients, there is a large number of alternative treatments that deserve consideration and referral to a pain management center should be contemplated, sooner rather than later. Invasive treatments may be considered when patients have failed to obtain adequate relief from other treatment approaches. These include sympathetic nerve blocks, which may provide temporary relief in patients with PHN but typically do not provide longer-lasting benefits.[86] Based on a review of 77 patients, it was reported that stellate ganglion blocks provided "good" pain relief in 50% of PHN patients who had pain for less than 1 year but in only 25% of patients who had pain for more than 1 year.[87] Similar data have also been presented by Winnie and Hartwell,[88] comparing sympathetic nerve blocks done within 2 months of the onset of zoster with blocks done more than 2 months after onset. Unfortunately, both of these studies were uncontrolled, making it impossible to distinguish greater efficacy of earlier treatment from the natural history of pain resolution in herpes zoster and PHN.

A study examining intrathecal administration of methylprednisolone[89] in patients with PHN received considerable attention because of the dramatic benefits that were described. However, intrathecal administration of methylprednisolone is not approved by the FDA and the well-known risks of intrathecal steroids include neurologic complications and adhesive arachnoiditis.

An uncontrolled study of spinal cord stimulation in 28 patients with PHN demonstrated long-term benefits in 82%, including pain relief of pain and improvements in daily functioning.[90] The authors reported that spontaneous improvement was ruled out by recurrence of pain following inactivation of the spinal cord stimulator. Confirmation of the benefits of spinal cord stimulation in patients with PHN will require use of adequate control groups.

It is important to conclude by emphasizing that the medications and invasive treatments that are currently available are rarely associated with the complete relief of PHN and evidence of their beneficial effects on quality of life is limited. Medical and invasive management of the patient with PHN should therefore be considered components of a more comprehensive treatment approach, which may include various nonpharmacologic treatments such as psychological counseling.[91]

KEY POINTS

- Herpes zoster (shingles) is caused by reactivation of the varicella-zoster virus (VZV), which establishes latency in sensory ganglia after primary infection (chicken pox).
- The characteristic unilateral dermatomal vesicular rash of herpes zoster heals within 2 to 4 weeks and is accompanied by pain in the majority of patients.
- Older age is associated with an increased risk of herpes zoster because of an age-associated decline in VZV-specific cell-mediated immunity.

- Antiviral therapy with acyclovir, famciclovir, valacyclovir, or brivudin in patients with herpes zoster inhibits viral replication and has been shown to reduce the duration of viral shedding, hasten rash healing, and decrease the duration of pain.
- The supplementation of antiviral therapy with opioids or corticosteroids may provide additional pain relief in herpes zoster patients with moderate to severe acute pain.
- Peripheral, sympathetic, and epidural nerve blocks with local anesthetics and/or corticosteroids appear to relieve acute pain in patients with herpes zoster, but their role in preventing PHN is uncertain because there are few randomized placebo-controlled trials.
- Postherpetic neuralgia refers to pain that continues after healing of the herpes zoster rash. This peripheral neuropathic pain condition causes substantial distress and disability and can last for years.
- Well-established risk factors for PHN in patients with herpes zoster include older age, more intense acute pain, more severe rash, and a prodrome of dermatomal pain before the rash appears.
- It is likely that different peripheral and central mechanisms contribute to PHN, and that the qualitatively different types of pain that characterize PHN have different underlying mechanisms.
- The efficacy of gabapentin, high-concentration capsaicin patch, lidocaine patch 5%, pregabalin, tramadol, tricyclic antidepressants, and opioid analgesics has been demonstrated by the results of RCTs in patients with PHN, and these medications provide an evidence-based approach to treatment. Combination therapy with opioids-gabapentin or nortriptyline-gabapentin may be more effective than either drug alone.

REFERENCES

Access the reference list online at http://www.expertconsult.com