Treatment and Prevention of Postherpetic Neuralgia

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There have been 4 recent major advances in the treatment of postherpetic neuralgia (PHN) that are based on the results of randomized, controlled trials. These advances are the demonstrations that gabapentin, the lidocaine patch 5%, and opioid analgesics are efficacious in patients with PHN, and the report that nortriptyline and amitriptyline provide equivalent analgesic benefits for patients with PHN but that nortriptyline is better tolerated. The results of these clinical trials are briefly reviewed, and their implications for the treatment of patients with PHN are discussed. Despite these treatment advances, many patients remain refractory to current therapy, and the prevention of PHN has therefore become an important focus of current research. Research on administration of the varicella-zoster vaccine to prevent herpes zoster and on treatment of patients who have herpes zoster with combined antiviral and analgesic therapy to prevent PHN is discussed.

Herpes zoster presents as a rash of 2–3 weeks duration in immunocompetent patients that is accompanied by moderate or severe pain [1]. In some patients, pain does not resolve when the rash heals but continues for weeks and, sometimes, for months or years; this persistent pain is termed “postherpetic neuralgia” (PHN) [2–4]. Although a variety of definitions of PHN have been used by clinicians and investigators, the results of recent studies suggest that the pain associated with herpes zoster has 3 phases: an acute herpetic neuralgia that accompanies the rash and lasts for ∼30 days after the onset of rash, a subacute herpetic neuralgia that lasts for 30–120 days after the onset of rash, and PHN, defined as pain that persists for ≥120 days after the onset of rash [2, 5, 6].

There have been no systematic attempts to investigate the prevalence of PHN, and estimates of the point prevalence have ranged from 500,000 to 1 million in the United States [7, 8]. The likelihood of developing PHN increases dramatically with age; therefore, most patients with PHN are elderly. The clinical significance of herpes zoster and PHN is supported by data demonstrating that PHN has a substantial negative impact on patients’ quality of life [4]. For example, patients with PHN attending a Liverpool, United Kingdom, pain clinic had visited their physicians an average of 18 times (range, 0–69 times) for treatment of pain, and more than one-half of these patients had been unable to perform their usual activities for up to 16 years [9]. In this article, we review recent major advances in the treatment of PHN and then discuss prospects for its prevention.

RECENT ADVANCES IN THE TREATMENT OF PHN

Since publication of the first randomized, controlled trials in the early 1980s, tricyclic antidepressants (TCAs) have been considered the first-line treatment for patients with PHN [10]. The efficacies of gabapentin, lidocaine patch 5%, and opioid analgesics for PHN have now also been demonstrated by the results of randomized, controlled trials. These 4 medications provide the clinician with an evidence-based approach to the treatment of PHN that was not available until very recently.

The initial choice of these medications should be guided by the patient’s comorbidities, the drugs’ adverse event profiles, and patient preference, especially because there are no replicated data demonstrating superior effectiveness of one class of drug over another. In general, we consider gabapentin and lidocaine patch 5% to be first-line treatments for PHN and opioid analgesics and TCAs to be second-line treatments. This is because opioid analgesics and TCAs generally have poorer
tolerability and require greater caution in patients with PHN (who are often elderly) and also because gabapentin and lidocaine patch 5% have been approved by the US Food and Drug Administration for the treatment of PHN.

**Gabapentin.** Patients with PHN have been treated with anticonvulsant medications, such as carbamazepine, for many years. Gabapentin, a second-generation anticonvulsant, was recently demonstrated to provide significant benefits when compared with placebo in the 2 largest controlled clinical trials involving PHN ever conducted [11, 12]. In these trials, treatment with gabapentin at daily doses of 1800–3600 mg was associated with a statistically significant reduction in daily pain ratings as well as improvements in sleep, mood, and quality of life.

The side effects of gabapentin include somnolence, dizziness, and (less commonly) mild peripheral edema; these may require dose adjustment but usually not treatment discontinuation. Gabapentin may cause or exacerbate gait and balance problems and cognitive impairment in elderly patients. Dosage adjustment of gabapentin is necessary in patients with renal insufficiency, but its generally excellent tolerability, safety, and lack of drug interactions distinguish it from the other orally administered medications used for treatment of PHN.

To reduce side effects and increase patient compliance with treatment, gabapentin should be initiated at low dosages (100–300 mg in a single dose taken at bedtime or 100 mg taken 3 times per day) and then titrated by 100 mg 3 times per day, as tolerated. In patients who develop dose-limiting side effects, further titration may be accomplished by titrating the bedtime dose until the patient accommodates to the side effects. The target dosages studied in the 2 controlled trials ranged from 1800 mg to 3600 mg per day. When partial relief of pain occurs at a dosage of 1800 mg per day, titration can be continued to 3600 mg per day (1200 mg 3 times per day), as tolerated. It is rare that patients who report the complete absence of any pain relief at a dosage of 1800 mg per day will obtain pain relief after further dose escalation, but, for a few patients, pain relief does begin only at higher dosages. It is important to recognize that, because of patient variability in gabapentin absorption, the final dosage should be determined on the basis of either complete pain relief, which is rare, or unacceptable side effects that do not resolve over a few weeks.

**Lidocaine patch 5%**. There are 2 published, double-blind, vehicle-controlled, randomized trials of lidocaine patch 5% for treatment of PHN [13, 14]. In these studies, patients with PHN who have allodynia (i.e., pain in the affected dermatome in response to an innocuous stimulus) obtained statistically significantly greater pain relief with lidocaine patch 5% compared with vehicle-control patches that contained no lidocaine. The results of a recent open-label trial demonstrated statistically significant reductions associated with lidocaine patch 5% treatment in the interference of pain with daily activities [15]. 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 and rash). Systemic absorption is minimal but must be considered in patients receiving orally administered class 1 antiarrhythmic drugs, such as mexiletine.

Treatment with the lidocaine patch 5% consists of the application of a maximum of 3 patches per day for a maximum of 12 h applied directly to the area of maximal PHN-associated pain and allodynia, which typically overlaps the primary affected dermatome. Lidocaine patch 5% is not approved for patients with herpes zoster, and it should not be used for patients with open lesions, because the available formulation is not sterile. Of importance, whether the patient obtains satisfactory relief from lidocaine patch 5% will usually be apparent within 2 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 intravenously administered morphine with placebo [16]. By providing evidence that PHN-associated 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. Two double-blind, placebo-controlled, randomized trials of oral opioid analgesics for treatment of PHN have now been published. In these studies, when compared with placebo, controlled-release oxycodone titrated to a maximum dosage of 60 mg per day provided statistically significant benefits with regard to pain, disability, and allodynia [17], and controlled-release morphine titrated to a maximum dosage of 240 mg per day provided statistically significant benefits with regard to pain and sleep but not physical functioning and mood [18]. One of these studies was a 3-period crossover trial in which opioid analgesics were compared with TCAs as well as placebo. In this trial, patients preferred treatment with opioid analgesics when compared with TCAs and placebo, despite a greater incidence of side effects during opioid treatment [18].

The most common side effects of opioid analgesic therapy are constipation, sedation, and nausea. In elderly patients treated with opioid analgesics, cognitive impairment and problems with mobility can occur, and there is an increased risk of hip fracture. Opioid analgesics must be used very cautiously by patients with a history of substance abuse or suicide, and accidental death or suicide can occur in association with overdose. Patients treated with opioid analgesics may develop analgesic tolerance (i.e., a reduction in analgesic benefit over time), although a stable dose 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
use of the 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 very low in patients with PHN, who are generally elderly, and concerns about abuse do not justify refraining from the use of opioid analgesics for PHN.

There are numerous short- and long-acting opioid analgesics available. Treatment can begin with a short-acting medication at morphine oral equianalgesic dosages of 5–15 mg every 4 h, as needed; after 1–2 weeks of treatment, the patient’s 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. Although there is no maximum dosage of opioid analgesics with careful titration and monitoring, evaluation by a pain specialist may be considered when morphine equianalgesic dosages exceeding 120 mg per day are contemplated.

TCAs. 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" [10]. Amitriptyline is clinically the most widely used TCA for treatment of PHN because it has been the most extensively studied TCA for PHN and other neuropathic pain syndromes. However, amitriptyline is poorly tolerated and contraindicated in elderly patients [19, 20]. In one of the very few randomized, double-blind trials that have compared 2 different treatments for patients with PHN, nortriptyline demonstrated equivalent efficacy to amitriptyline but was better tolerated [21]. On the basis of the results of this study, nortriptyline should now be considered the preferred TCA for treatment of PHN; desipramine may be used for patients who experience excessive sedation with nortriptyline.

Despite the efficacy of TCAs for the treatment of PHN, their cardiac toxicity [22] and side effect profile require considerable caution when treating older patients with PHN. Dry mouth is the most common side effect, occurring in up to 40% of patients treated with amitriptyline and 25% of patients treated with nortriptyline. Constipation, sweating, dizziness, disturbed vision, and drowsiness are reported by as many as 20%–30% of patients treated with amitriptyline and 5%–15% of those treated with nortriptyline. All TCAs must be used very cautiously by patients with a history of cardiovascular disease, glaucoma, urinary retention, and autonomic neuropathy, and a screening electrocardiogram to check for cardiac conduction abnormalities is recommended before beginning TCA treatment, especially for patients >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 elderly patients. TCAs can block the effects of certain antihypertensive drugs and interact with drugs metabolized by P450 2D6 (e.g., cimetidine and type 1C antiarrhythmics). Because all selective serotonin reuptake inhibitors inhibit P450 2D6, caution is necessary in the concomitant administration of TCAs and serotonin reuptake inhibitors to prevent toxic TCA plasma concentrations.

To decrease side effects, all TCAs should be initiated at low dosages (10–25 mg in a single dose taken 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 the antidepressant effect, but there is no evidence of this from controlled clinical trials. Consequently, TCAs should be titrated to dosages of at least 75–150 mg per day. For titration at more than 100–150 mg per day, blood levels and electrocardiograph findings 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.

Sequential and combination treatment with first- and second-line medications. There have been few clinical trials in which the medications we have discussed have been directly compared with each other [18, 21]. Such comparisons would not only make it possible to directly determine whether treatments vary in efficacy, safety, and tolerability, but, when conducted with the same patients, they 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 3-period, placebo-controlled crossover trial, which suggests that, when a patient has not responded to one of these types of medication, he or she may still respond to the other [18].

The randomized, controlled trials of the 4 first- and second-line treatments for PHN (gabapentin, lidocaine patch 5%, opioid analgesics, and TCAs) all examined the efficacy of single medications versus placebo or a comparison drug. Combination therapy, however, is the norm in the clinical setting. Unfortunately, there are no data regarding the additive or synergistic benefits of combination treatment, and it is not known which patients are most likely to benefit from what medication combinations. Disadvantages of combination therapy include an increased risk of side effects as the number of medications is increased and the difficulty identifying which medication is responsible for side effects. Ideally, combination therapy would involve a “rational polypharmacy” that is based on an understanding of the pathophysiological mechanisms of a patient’s PHN, and such an approach to the treatment of PHN may become possible as understanding of its mechanisms increases [23].
Beyond first- and second-line therapy. An unknown percentage of patients with PHN will not respond to these first- and second-line treatments when used alone and in combination. For these unfortunate patients, there are many alternative treatments that deserve consideration, and referral to a pain management center should be contemplated sooner rather than later [24]. Invasive treatments may be considered when patients have not obtained relief from other treatment approaches. These include spinal cord stimulation [25] and intrathecal administration of methylprednisolone [26], which is not approved by the US Food and Drug Administration and carries the risk of arachnoiditis and other neurologic complications.

It is important to emphasize that the medications that are currently available are rarely associated with the complete elimination of PHN, and evidence about their beneficial effects on quality of life is limited. Pharmacological treatment of patients with PHN should therefore be considered one component of a more comprehensive treatment approach, which may include various nonpharmacological treatments, such as psychological counseling.

PROSPECTS FOR THE PREVENTION OF PHN

Because PHN can be refractory not only to first- and second-line treatment but also to all other therapies, its prevention is a very important goal. In recent research, older age, greater acute pain during herpes zoster, and greater rash severity have been identified by independent groups of investigators as risk factors for PHN [4, 27]. These risk factors provide substantial support for the conclusion that there is a greater risk of PHN in patients with more severe acute infections, which are accompanied by greater neural damage. It has been proposed that this neural damage in patients with herpes zoster contributes prominently to the development of PHN, and that PHN might therefore be prevented by reducing the severity of the herpes zoster infection [2, 28].

One method of reducing the severity of the acute infection and limiting the degree of neural damage it causes involves treatment with the antiviral agents acyclovir, famciclovir, and valacyclovir. By inhibiting viral replication, these antiviral agents attenuate the severity of the acute herpes zoster infection—specifically, the duration of viral shedding is decreased, rash healing is hastened, and the severity and duration of acute pain is reduced. The results of randomized, controlled trials and meta-analyses have also demonstrated that antiviral therapy in herpes zoster significantly reduces the risk of prolonged pain [29–35]. Although the results of each of these studies taken singly can be challenged, the consistency of the findings provides strong support for the use of antiviral agents in the treatment of herpes zoster. Antiviral therapy has been recommended in several recently published literature reviews and treatment guidelines for patients with herpes zoster who are older, have moderate or severe rash, have moderate or severe pain, or have ophthalmic involvement [1, 3].

Although the reduction in the risk of PHN that accompanies antiviral therapy in patients with herpes zoster is both clinically and statistically significant, antiviral therapy does not prevent PHN in all patients. Almost 20% of patients aged ≥50 years continue to have pain 6 months after rash onset, despite treatment with famciclovir or valacyclovir beginning ≤72 h after the onset of rash [33–35]. How, then, can the risk of PHN be further reduced, beyond that currently achieved by antiviral therapy? Although it is possible that new antiviral agents with greater efficacy will be developed, a different strategy for preventing PHN is to supplement antiviral treatment. Unfortunately, the results of a number of studies that have examined the long-term benefits of corticosteroids, TCAs, and nerve blocks in patients with herpes zoster are either equivocal or in need of replication [36–39]. Nevertheless, there are compelling reasons to predict that combining antiviral therapy with effective relief of acute herpes zoster pain (for example, by administration of opioid analgesics or gabapentin) will further lessen the risk of PHN beyond that achieved by antiviral therapy alone. The basis for this hypothesis is provided by the very well-replicated relationship between acute pain severity and PHN and by recent research on the pathophysiological mechanisms of PHN [4, 23, 27, 28]. But even if there were no benefit with respect to the later development of PHN, the effective relief of acute pain in patients with herpes zoster is clearly a very desirable treatment goal in itself.

PROSPECTS FOR THE PREVENTION OF HERPES ZOSTER

Although there are ongoing trials of interventions designed to prevent PHN by analgesic and other treatments of patients with herpes zoster, another approach to the prevention of PHN involves the use of a varicella vaccine to prevent varicella and herpes zoster. A live, attenuated varicella vaccine is effective in preventing against varicella and its complications [40]. Vaccine uptake in the United States among children aged 19–35 months in 2001 was 76%, and varicella epidemic curves have been substantially reduced in regions where the vaccine is accepted [41, 42]. What effect will varicella vaccination have on the incidence of herpes zoster and PHN? The incidence of herpes zoster and PHN may significantly decrease as vaccinated children become older adults and as adults who are latently infected with wild-type varicella-zoster virus (VZV) die, because the vaccine virus may be less likely to establish latency and reactivate than wild-type VZV. This idea is supported by the observation that herpes zoster was less common among leukemic
children who received the vaccine than among leukemic children with a past history of varicella [43].

However, some investigators have noted that the incidence of herpes zoster (and perhaps PHN) could increase among individuals latently infected with wild-type VZV as the incidence of varicella decreases [44]. They reason that a decrease in the incidence of varicella will reduce the population’s exposure to VZV, prevent subsequent immune boosting to VZV, and increase the risk of VZV reactivation [45].

Currently, most individuals are latently infected with wild-type VZV and at risk for herpes zoster. A fundamental epidemiological feature of herpes zoster is the marked increase in its incidence with aging [4]. The age at which the sharpest increase in herpes zoster occurs is 50–60 years, a consequence of the decline in VZV-specific cell-mediated immunity that occurs with aging. Administration of a live, attenuated varicella-zoster vaccine to older adults [47]. If such immunization reduces the incidence or severity of herpes zoster, then a reduction in the incidence or severity of PHN would be expected. The results of ongoing clinical trials will determine whether immunization of older adults with a varicella-zoster vaccine is efficacious [48]; if it is, and if vaccine use becomes widespread among older adults, then PHN may become so rare that it ceases to be a feared complication of herpes zoster.

References