CURRENT MANAGEMENT OF POSTHERPETIC NEURALGIA

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BACKGROUND—The herpes zoster rash occurs when a dormant varicella zoster virus reactivates in dorsal root and cranial nerve ganglia. Pain that persists in the region where this rash occurred after the cutaneous lesions have healed is termed postherpetic neuralgia (PHN). A wide variety of therapies has been used with varying degrees of success to prevent the occurrence of PHN and to reduce pain with established PHN.

REVIEW SUMMARY—In this review, we discuss the clinical presentation of PHN, current strategies for the prevention and management of this disease, and observations that have increased our understanding of the neural mechanisms involved in PHN.

CONCLUSIONS—Several classes of drugs are effective in attenuating the pain and hyperalgesia caused by PHN, but no single drug leads to the complete relief of symptoms. Additional research is needed to improve treatment strategies and define the role of invasive pain management techniques in cases where PHN is associated with intractable pain.

KEY WORDS postherpetic neuralgia, herpes zoster, neuropathic pain, treatment


The incidence of postherpetic neuralgia (PHN), one of the most common forms of neuropathic pain, increases significantly in patients as their age advances. Not only is PHN a relatively common cause of chronic pain in people over the age of 60 years, but the severity and duration of associated pain also increase with patients’ age. Retrospective population data from Liverpool, England suggest that nearly one quarter of elderly patients experience herpes zoster outbreaks, and 15% of these patients, or 3.6% of elderly people, develop PHN at a median age of 60 years (1). Herpes zoster outbreaks are usually nonrecurrent, with an incidence of less than 5% for repeat episodes (2). Epidemiologic studies report that the annual incidence of herpes zoster increases from 0.4 to 1.6 cases per 1000 among healthy patients less than 20 years old to 4.5 to 11 cases per 1000 in patients 80 years and older (3). A prospective study examined the incidence of PHN after a single episode of herpes zoster and determined the probability of developing PHN in groups under and over age 60 years (3,4). Although only 2% of all patients younger than 60 years continued to have pain 3 months after the initial zoster outbreak, the odds ratio of having continued pain at 12 months increased 2.33 per each 10 years of additional age. Almost 50% of patients over 70 years of age have pain lasting more than 1 year after the onset of zoster-associated rash.

A summary by Kost et al (3) of the epidemiology of PHN noted that age-dependant decreases in cell-mediated immunity (CMI) might contribute to the increased incidence with increasing age. The incidence of PHN has also been found to be much higher in adults with cancer, in those with human immunodeficiency virus (5), and in patients experiencing psychologic and physiologic stress (6).

DIAGNOSIS

Herpes zoster presents as an acute rash that progresses from erythema to vesicular eruptions in one or more adjacent dermatomes. Crusting of the lesions usually occurs within 10
Almost 50% of patients over 70 years of age have pain lasting more than 1 year after the onset of zoster-associated rash.

The pain of PHN is most frequently described as a constant burning sensation with frequent paroxysmal lancinating or electric shock-like sensations. Patchy allodynia, hyperesthesia, and hypoesthesia can be present in varying combinations in the affected region. Patients frequently report behaviors designed to protect the affected area from normally nonnoxious stimuli. Contact with bed sheets, clothing, and even exposure to the wind can exacerbate the pain. The ongoing spontaneous pain and, particularly, the allodynic component of PHN can be debilitating and can lead to depression, social isolation, and increasing health care utilization.

PREDICTORS

An accurate estimation of the risk of developing PHN enables informed therapeutic decision making. Furthermore, risk assessment may facilitate preventive therapy and help minimize a patient's disability, psychological distress, and use of health care resources.

Whithel et al (7) analyzed data from six randomized, double-blind, controlled trials to identify the factors that influence the persistence of herpes zoster pain. The six trials included 2367 patients who were treated with acyclovir, valacyclovir, netivudine, or a placebo. The investigators found that the median duration of pain associated with herpes zoster increased from 21 days in patients less than 50 years old to 101 days in patients 50 or more years old. In the valacyclovir studies, the presence and intensity of prodromal pain were highly predictive of prolonged zoster pain, regardless of age. Interestingly, neither the sex of the patient nor the time from rash onset to antiviral treatment significantly influenced zoster pain resolution.

Although it is well established that advancing age increases the risk of developing PHN, six other predictors of the development and persistence of PHN have been identified. First, the results of several studies examining persistence of pain over a 6-month follow-up period suggested that patients with the most severe acute herpes zoster pain have the greatest risk of suffering persistent zoster pain and developing PHN (8–10). Many researchers believe that the relationship between the severity of acute pain and prolonged herpes zoster pain has been established (11).

The appearance of severe cutaneous lesions, which reflect the severity of the acute infection, is a second predictor of prolonged pain (9,11). This finding suggests that pain may be related to the number of affected vesicles and the proportion of dermatome affected.

Third, Nurmikko and Bowsher (12) reported that scarring in the affected dermatome may distinguish patients who will develop PHN from those who have pain that will attenuate. The healing of the herpes zoster rash often causes scarring, and, because scarring is likely associated with greater rash severity, this observation supports the association between greater cutaneous manifestations during infection and prolonged pain. Interestingly, Rowbotham and Fields (13) showed that PHN patients with allodynic pain demonstrate less-severe scarring. This may imply that scarring and the preceding severe rash are related to specific kinds of PHN pain.

Fourth, sensory dysfunction in the affected dermatome during acute herpes zoster might predict development and persistence of PHN. Based on comparisons of sensory changes in patients with and without PHN after acute herpes zoster, Nurmikko and Bowsher (12) reported that patients with sensory changes, such as hyperesthesia and elevated thermal and vibration thresholds in the affected dermatome compared with the contralateral dermatome, have an increased risk of prolonged pain. These investigators concluded that PHN is primarily a deafferentation pain syndrome resulting from plastic changes in the central nervous system (CNS). In addition, Rowbotham and Fields (14) observed a direct correlation between intensity of pain and normal thermal sensibility and hypothesized that activity in the intact nociceptors innervating the affected PHN sites may play an important role in the mechanisms of PHN. The relative discrepancy in these hypotheses may be resolved by studies that suggest the mechanisms of pain in PHN may vary among patients.

Fifth, a more intense magnitude and duration of humoral and cell-mediated response during acute herpes zoster might also predict prolonged pain, suggesting a relationship between the severity of acute infection and the magnitude of the immune response (15,16). This is supported by the fact that varicella zoster virus (VZV) cell-mediated immune responses reach maximum capacity at 1 to 2 weeks after the onset of herpes zoster, which is often the time of maximal
infection. Furthermore, Glaser and Kiecolt-Glaser (17) propose a relationship between antibody titers and the extent of viral reactivation in herpes zoster and Epstein-Barr virus. Additional studies have also found a less intense immune response to VZV in patients treated with antivirals.

Finally, several investigators identified the combination of painful prodrome and fever greater than 38°C during acute herpes zoster as a predictor of prolonged pain (18,19). Together, these predictors, which can be viewed as components of severe infection, support the notion that the severity of neural dysfunction during acute herpes zoster contributes to the development of PHN.

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**Postherpetic neuralgia is generally diagnosed when pain lasts longer than 1 month after the rash heals.**

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Psychosocial factors also influence whether a patient experiences PHN. For example, Pilowsky (20) suggested that patients with prolonged pain may have premorbid personality traits or be undergoing stressful life events. In cross-sectional studies, PHN patients presented with a larger number of anxiety-associated symptoms and rated prior pain experiences as more intense than did herpes zoster patients whose pain did not persist (21). Furthermore, retrospective studies revealed that patients who reported suffering other diseases with or without concurrent psychological stress at the onset of herpes zoster were at substantially higher risk of developing PHN, altered daily activities, and a decreased sense of well-being than were patients without additional physical or psychological burdens (22). Similarly, in a prospective study, Dworkin et al (8) found that patients with PHN were more likely to exhibit symptoms of depression, anxiety, and lower life satisfaction during acute infection than were patients who failed to develop PHN. In summary, both organic and psychological factors may play a role in the genesis of PHN. Thus, Dworkin and Portenoy (11) propose a diathesis stress model in which the risk of developing PHN increases with greater severity of neural damage as well as with escalations of psychosocial stress.

**PATHOPHYSIOLOGY**

VZV is a double-stranded DNA virus of the herpes family. Primary varicella infection commonly manifests as chickenpox, followed by a latent noninfectious phase during which the virus survives in cranial nerves and dorsal root ganglia. Conditions that depress cell-mediated immunity, particularly generalized immunosuppressive states and advancing age, predispose patients to viral reactivation and replication (23). Zoster can be produced when the reacti- vated virus replicates and migrates along peripheral sensory pathways. Acute zoster causes cutaneous inflammation and partial denervation in a dermatomal distribution (10) as well as inflammation, necrosis, and fibrosis in the dorsal root ganglia. Inflammatory changes in peripheral nerves can last for months and lead to demyelination, Wallerian degeneration, and fibrosis. In postmortem studies, Watson et al (24) found demyelination and loss of axons in the peripheral nerve and sensory roots of PHN patients with and without associated pain. Dorsal horn atrophy, cell loss, and demyelination with fibrosis, however, occurred only in those with pain. VZV in tissue culture can induce spontaneous firing in neurons that would normally be electrically silent (25). Loss of myelinated afferent neurons and neuronal plasticity in the dorsal horn may, thus, result in uninhibited and amplified activity in unmyelinated primary afferents, which, in turn, may lead to the pain associated with PHN.

Several investigations have attempted to determine whether pain in PHN results predominantly from deafferentation or from the activity of remaining peripheral nociceptors (current evidence supports both conceptual mechanisms) (26–28). These studies suggest that subtypes of PHN can be distinguished based on their neural mechanisms and that the presence or absence of deafferentation, sensory loss, and hyperalgesia may be measurable clinical indicators that will help delineate these subtypes. Identification of these subtypes may have therapeutic implications if the response to different treatments correlates with the neural mechanism involved.

Rowbotham et al (29) proposed the following three subtypes of PHN based on quantitative sensory examination of patients: (1) the irritable nociceptors group, with mechanical allodynia (pain to light brushing of skin) and normal thermal sensation or thermal hyperalgesia; (2) the central reorganization group, with mechanical allodynia and thermal sensory deficits; and (3) the deafferentiation group, with ongoing pain without allodynia in a region marked by profound sensory loss.

These investigators believe that persistent abnormal activity from damaged nociceptors or sensitization of the undamaged nociceptors plays an important role in the development of pain in PHN subtype 1 (29). The concept of irritable nociceptors implicates that neuropathic pain results from peripheral sensitization and spontaneous activity. In these patients, a specific peripheral mechanism, such as abnormal activity in the C-fiber afferents, may be necessary to induce central sensitization and maintain mechanical allodynia.

In patients with PHN subtype 2, allodynia to mechanical stimuli is often associated with deficits in thermal detection of warm or cool stimuli. Alternatively, facilitated pain states may exist in patients with deafferentation without allodynia from CNS hyperexcitability, loss of inhibitory large fiber afferents, or loss of CNS inhibitory cells (subtype 3).

Pappagallo et al (30) performed quantitative sensory testing on the affected and contralateral sides of 63 patients who had PHN in different distributions and for varying durations. These investigators categorized more than 50% of their pa-
patients as subtype 2, with the rest approximately equally distributed between subtypes 1 and 3 and found significant differences among the groups depending on the duration of pain. In addition, the relative contribution of peripheral and CNS mechanisms varied among individual patients and over the duration of PHN. The sensitization of cutaneous nociceptors was more prevalent early in the disease (less than 1 year), indicating that CNS mechanisms may predominate later. Information obtained upon careful sensory examination, therefore, may be useful in selecting therapies that are targeted at the predominant mechanism maintaining pain in individual patients. For example, patients with relatively less deafferentation and more cutaneous sensitization may respond well to topical therapies. Researchers hope that the identification of mechanistic subtypes and development of mechanism-specific therapies will allow physicians to tailor treatment to individual patients.

TREATMENT

The efficacy and safety of several of the numerous proposed treatments for PHN are difficult to evaluate, because small sample sizes, heterogeneous populations, inadequate controls, ambiguous outcome definitions, and short-term follow-up have limited pertinent studies. Inclusion of adequate controls is of particular relevance to study design, because PHN frequently resolves spontaneously over time (24), and diminution of pain might incorrectly be attributed to treatment-specific effects.

The response of individual patients to present therapies can be hard to predict, and, in some patients, effective analgesia can be very difficult to achieve. In fact, as many as 40% to 50% of patients with PHN do not obtain satisfactory relief of pain despite the use of presently available treatments (31,32). There are, however, several classes of drugs with proven efficacy and favorable safety profiles that are considered first-line treatments for established PHN. Invasive approaches and alternatives associated with relatively less supportive evidence should be reserved for patients who do not respond to first-line treatments.

Medical Therapies

Oral therapies – Kanazi et al (33) reviewed randomized controlled trials (RCTs) of tricyclic antidepressants, gabapentin, and controlled-release oxycodone for PHN and reported that these medications all provide pain relief with a similar efficacy that is better than that achieved with a placebo. In addition, nortriptyline is equianalgesic to but associated with fewer side effects than amitriptyline.

A quantitative systematic analysis of the relative efficacy and incidence of adverse effects of antiseizure and antidepressant drugs used to treat pain in diabetic neuropathy and in PHN considered three RCTs that compared the use of antidepressants (amitriptyline in two and desipramine in the other) versus placebo to treat PHN (34). This analysis revealed a number needed to treat (NNT) of 2.1 (95% confidence interval, 1.7 to 3) for at least 50% pain relief, which was significantly better than placebo. One study comparing gabapentin with placebo yielded a NNT of 3.2 (2.4 to 5). Overlapping confidence intervals prevented determination of which drug class was more effective for either condition, but additional pooling of data revealed a NNT of 2.9 (2.4 to 3.7) to achieve 50% pain relief across both pain states and both drug classes. The incidence of minor side effects was the same for both drug classes, but the occurrence of side effects leading to withdrawal from trials was considerably higher for tricyclic antidepressants, with a number needed to harm (NNH) of 17 (range, 11 to 43). The ratios between treatment-specific benefit and treatment-specific major harm were 5 for tricyclic antidepressants and 8 for gabapentin. Thus, for every five patients obtaining at least 50% pain relief from tricyclic antidepressants, one will experience adverse effects leading to discontinuation of the drug versus one out of eight patients treated with gabapentin. There was no significant difference in relative risk of major adverse effects between gabapentin and placebo, and no difference was noted in efficacy between gabapentin and the older drugs phenytoin and carbamazepine. Gabapentin has found widespread use in the treatment of a variety of neuropathic pain conditions, likely resulting from its established efficacy and favorable adverse-effect profile compared with phenytoin and carbamazepine. Other recently developed antiepileptics such as lamotrigine have not been thoroughly investigated by RCT for the treatment of PHN. The efficacy of selective serotonin reuptake inhibitors has not been established by RCT.

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**Gabapentin has found widespread use in the treatment of a variety of neuropathic pain conditions**

Sindrup and Jensen (35) achieved similar results in their determination of the NNT for several drugs based on available RCTs. These investigators calculated a NNT of 2.3 for tricyclic antidepressants, 2.5 for oxycodone, 3.2 for gabapentin, 5.3 for capsaicin, and no efficacy for dextromethorphan. Additional trials are needed to determine the efficacy of the combinations of these agents that are often used in clinical settings.

Confirmatory evidence continues to accrue in support of the efficacy and tolerability of gabapentin. In 2001, Rice and Maton (36) conducted a large multicenter, double-blind RCT and reported that gabapentin treatment led to significant improvements in multiple validated pain and quality of
life measures and was associated with few and generally mild side effects.

Tramadol possesses opioid properties and also affects the reuptake of amines in a manner similar to the mechanism of tricyclic antidepressants. A noncontrolled study suggests that tramadol can be effective in reducing PHN pain while avoiding the adverse effects associated with more potent opioid agonists (37), and one RCT has revealed the efficacy of this agent in other neuropathic pain states, such as diabetic neuropathy (38).

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**Early antiviral therapy during the acute zoster attack decreases the duration of viral shedding, accelerates rash healing, and reduces the duration of acute pain and postherpetic neuralgia.**

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The efficacy of opioids to treat neuropathic pain has been intensely debated (39,40). In one study, however, the observed analgesic effect of OxyContin was not accompanied by concurrent changes in mood (40). In a randomized, double-blind, placebo-controlled crossover study, the analgesic and cognitive effects of tricyclic antidepressants (TCAs) and opioids on PHN have been compared (41). Both opioids and TCA reduced pain more than placebo. Some patients responded better to the opioids, whereas others responded better to the TCA. The study indicated that opioids and TCA act via independent mechanisms and may have variable effects in an individual patient with PHN. In addition, controlled-release morphine was not associated with significant cognitive deficits in this elderly population with PHN.

**Intravenous therapies** — Trials performed in a small number of PHN patients showed that intravenous and subcutaneous ketamine can reduce spontaneous and paroxysmal pain as well as allodynia (42,43). Ketamine is an n-methyl-d-aspartic acid (NMDA) receptor antagonist, and NMDA receptors are glutamate receptor subtypes believed to be involved in the central transmission of neuropathic pain. In these studies, however, significant side effects, such as fatigue, dizziness, mood changes, and infusion site problems, occurred in most subjects. These adverse effects presently limit the parenteral utility of ketamine.

Oral ketamine was reported to be efficacious for pain relief in a single patient with PHN without side effects (44). Anecdotal evidence also exists regarding the successful use of dextromethorphan, another NMDA antagonist, in PHN (45), but the efficacy of this agent has not been tested in an RCT (46). Eisenberg et al (47) found memantine, another NMDA antagonist, to be no better than placebo in treating PHN.

A double-blind RCT comparing intravenous lidocaine to saline showed reduction in PHN pain and allodynia with lidocaine (48). Lidocaine has similar efficacy when infused at 1 and at 5 mg/kg over 2 hours. In each case, lidocaine treatment led to significant pain reduction as well as contraction of the surface area where allodynia could be evoked. This finding is the basis for the use of oral mexiletine to achieve systemic sodium channel blockade and reduction of PHN pain in patients who respond to intravenous lidocaine. The overall efficacy of this strategy, however, has yet to be proved. Investigators have achieved promising results with another sodium channel blocker, flecaïnide, used with an intravenous infusion test followed by oral treatment for those who respond (49).

**Topical therapies** — In contrast to systemic analgesics, which have the potential for causing undesirable side effects, application of topical local anesthetics can reduce pain in PHN without significant systemic effects. Lidocaine gel (50), an eutectic (a mixture of chemicals with a lower melting point than that of the individual components) mixture of local anesthetics (EMLA) (51), and lidocaine-impregnated patches (52) applied to areas of pain and allodynia can significantly reduce constant pain as well as paroxysmal pain and allodynia. Continued use over several days can provide additional benefit beyond the acute relief obtained with initial use. The United States Food and Drug Administration has granted approval for the use of a 5% lidocaine patch for PHN, because there is established efficacy and apparently little risk with this treatment. The protection afforded by the patch vehicle itself against mechanical stimulation of allodynic skin is beneficial independent of the drug activity. Although many patients experience partial relief, complete relief usually does not occur, and some patients cannot continue therapy because of local skin irritation. The efficacy of topical local anesthetic for PHN over extended periods is unknown, because follow-up intervals have been limited in published studies.

The topical administration of capsaicin has also been suggested as a therapeutic option in the management of PHN. The exact mechanism of action of capsaicin is uncertain, but the drug causes release of substance P and other neuropeptides from nociceptive fibers and, with prolonged or repeated administration, can deplete the neuronal stores of neurotransmitters (53), leading to cessation of local nociceptive function (54). After preliminary studies suggested that capsaicin may be efficacious in reducing PHN (55,56), Watson et al (57) conducted a trial with 143 patients randomized to receive 0.075% capsaicin cream or placebo cream. Patients were followed for up to 2 years, and several patients enjoyed a significant and prolonged improvement in pain symptoms and functional measures. No serious adverse
effects were reported, but some patients experienced an intolerable burning sensation. The utility of this treatment is, thus, limited by the discomfort associated with initial nociceptor activation.

It seems that patients in whom well-preserved cutaneous primary afferents are the predominant mechanism of ongoing pain are both the most likely to benefit from and the least likely to tolerate capsaicin (27). Conversely, those who can best tolerate capsaicin are the least likely to benefit, because CNS mechanisms may have a predominant role. The discomfort associated with capsaicin might be averted if we create capsaicin analogues that would be effective without causing the initial nociceptor activation.

Interventional Therapies

Neural Blockade and Neuropathic Steroids – A report by Kotani et al (58) has sparked renewed interest and controversy regarding the use of intrathecal steroids for refractory PHN. Preliminary work had shown that intrathecal, but not epidural, methylprednisolone may be effective (59). Citing postmortem evidence of spinal cord inflammation and high levels of interleukin-8 in the cerebrospinal fluid of patients with PHN, the authors postulated that antiinflammatory treatment might reverse or retard PHN. They randomized 277 patients to receive intrathecal methylprednisolone plus lidocaine, lidocaine alone, or no treatment weekly for up to 4 weeks. All patients had suffered from persistent PHN for at least 1 year despite treatment with systemic diclofenac, antidepressants, and antiseizure medications, and all patients continued to have persistent pain before inclusion. Through 2 years of follow-up, the authors reported good or excellent relief of both spontaneous and allodynic pain in 90% of the steroid plus local anesthetic group versus 7% for the group receiving lidocaine alone and 3% for the no-treatment group.

If nonprescription analgesics do not work, consideration should be given to opioids and tricyclic antidepressants for symptomatic relief during the acute zoster episode.

In addition, they reported a significant reduction in the cerebrospinal fluid level of interleukin-8 in the steroid plus local anesthetic group only. Other authors have questioned the role of ongoing inflammation in established PHN and emphasize the possible risks associated with the intrathecal injection of available formulations of methylprednisolone (60,61). Although arachnoiditis, transverse myelitis, cauda equina syndrome, and other neurologic sequelae have been associated with intrathecal steroid administration (62), no such adverse events occurred in the trial conducted by Kotani et al.

Epidural injection of local anesthetic either intermittently or via continuous catheter is effective in reducing pain severity and duration during acute herpes zoster outbreaks (63–66). Although epidural injection to treat pain in PHN has been investigated less extensively (67,68), there is little evidence to suggest that epidural injections alter the course of established PHN aside from providing transient relief.

Winnie et al (69) postulated that providing analgesia and blockade of the sympathetic nervous system during acute herpes zoster may help prevent development of PHN. This led Manabe et al (65) to speculate that the epidural administration of local anesthetics might reduce the incidence of PHN. Two unblinded studies compared the duration of pain in patients receiving oral antiviral treatment in combination with epidural infusion of local anesthetic during acute herpes zoster to that in patients receiving oral antivirals alone (63,64). The epidural group clearly obtained more rapid resolution of acute pain, but only RCTs with long-term follow-up can establish whether this intervention can prevent PHN.

Although it is possibly efficacious for herpes zoster pain, selective blockade of the sympathetic nervous system with local anesthetic has not led to prolonged pain relief in established PHN (70). In a retrospective study of a small group of patients, Reiestad and colleagues (71,72) reported that infusion of a local anesthetic via a percutaneously placed interpleural catheter reduced pain severity and duration during acute herpes zoster and PHN. The role of intercostal peripheral injection of local anesthetic or steroid has not been established either retrospectively or by RCT, and cryotherapy of intercostal nerves has yielded poor retrospective results (73). In one series of subcutaneous dermal injection of local anesthetic and steroid in 3960 patients, 96% of patients obtained complete relief with repeated blocks over a 6-week follow-up period; however, no control group was included (74).

Neuroaugmentation and Neuroablation – Published reports regarding the efficacy of transcutaneous nerve stimulation systems (TENS) as treatment for PHN are inconclusive because they lack standardization of stimulation parameters and outcome measures (75). The use of spinal cord stimulation for relief of chronic PHN pain is supported by the experience of Spiegelmann et al (76), but others have found this technique disappointing (77). Electrical stimulation of the Gasserian ganglion with an implanted nerve stimulating system may be effective in certain kinds of chronic facial pain (78); however, Taub et al (79) reported no success when applying this treatment to four patients with PHN in an
uncontrolled study. Poor results have also been reported with the use of deep brain stimulation for PHN (80).

Overall, the experience with surgical ablative therapies for PHN has been discouraging. Skin excision, sympathectomy, peripheral neurolysis, myelotomy, cordotomy, and intracranial surgery were examined in a few patients before the widespread acceptance of antidepressant and anticonvulsant therapies (82). In light of the absence of supportive evidence and the potential for adverse effects, surgical ablative therapies for PHN have few advocates.

A retrospective review of the use of dorsal rhizotomy revealed a long-term success rate of approximately 30% (83,84). More varied, yet similar, overall results have been reported for the use of dorsal root entry zone operations to treat PHN (85–88). Moreover, a significant incidence of persistent ataxia has been associated with the dorsal root entry zone procedure.

Urgoisi et al (89) have used gamma knife radiosurgery as a noninvasive option for patients whose refractory PHN pain involved the trigeminal nerve. In this trial, radiation was directed at the root of the trigeminal nerve near the brainstem. The results in a series of 16 patients yielded a success rate of 44% (significant pain relief). There were no reports of adverse effects in this series, but in a preliminary report, the investigators noted that some patients experienced tactile hypesthesia (90).

**Behavioral Therapies**

We presently lack definitive clinical trials of psychologic interventions, such as biofeedback, for the treatment of PHN and chronic pain in general. A limited number of case series, however, suggests that biofeedback may improve the quality of life in patients with PHN (91).

**Acupuncture**

Acupuncture has not been shown in any RCT to be superior to placebo, sham treatment, or no treatment for PHN. One RCT with a small sample demonstrated no benefit with acupuncture versus mock transcutaneous nerve stimulation (92).

**PREVENTION**

Despite the availability of drugs that can reduce pain in PHN, the importance of preventing reactivation of herpes zoster and preventing the development of PHN when reactivation occurs cannot be understated. Antiviral medications, tricyclic antidepressants, and steroids have been used during acute herpes zoster outbreaks in attempts to reduce the subsequent incidence of PHN. Investigators have also turned attention to the use of vaccination as a means of reducing the incidence of herpes zoster recurrence and subsequent PHN.

Bowsheer (93) reported a randomized, double-blind, placebo-controlled trial of preemptive treatment with 25 mg amitriptyline per day for 90 days in patients over age 60 years with newly diagnosed herpes zoster. Prevalence of PHN at 6 months was reduced by more than 50%, with a NNT of 5.1. The fact that patients receiving amitriptyline were warned about the side effects of tricyclic antidepressants, however, may have compromised blinding. Also, the concurrent use of acyclovir was not controlled, and reduced pain occurred in patients treated with both drugs compared with those treated with placebo plus acyclovir.

Results of an RCT in immunocompetent patients with herpes zoster indicated that early antiviral therapy during the acute zoster attack decreases the duration of viral shedding, accelerates rash healing, and reduces the duration of acute pain and PHN (94,95). Two meta-analyses of double-blind, placebo-controlled trials revealed that acyclovir decreases the duration and incidence of PHN (10,96). Similarly, trials with famciclovir suggested that this drug reduces the duration of PHN (94,97).

Dworkin et al (95) assessed the efficacy and safety of famciclovir in 419 immunocompetent patients with uncomplicated herpes zoster in a multicenter, double-blind RCT. These investigators examined the effects of 500 or 750 mg doses three times a day for 7 days (initiated within 72 hours of rash onset) on viral shedding, cutaneous end points, acute pain, and duration of PHN. The median time to cessation of PHN in patients 50 years of age or older was 163 days in the placebo group versus 63 days in the 500 and 750 mg famciclovir groups. Furthermore, using the definition of PHN as pain persisting 30 days or 3 months after study enrollment, the intent to treat analyses showed reduced duration of PHN in acute zoster patients treated in each famciclovir group. NNT for prevention of PHN calculated from the data provided by the investigators for the 500 and 75 mg doses of famciclovir at 90 days was 21 and 18 and at 180 days was 11 and 9, respectively. These analyses suggest that treatment of acute herpes zoster patients with famciclovir reduces the risk and duration of PHN but may not have a significant effect on the incidence of PHN.

In a systematic review of 42 trials, Alper et al (98) analyzed the evidence supporting the hypothesis that PHN can be prevented by antiviral or other therapies. Four RCTs of oral acyclovir (800 mg five times daily; 692 patients) provided only marginal evidence of reduced pain at 1 to 3 months. Treatment was initiated within 72 hours after the appearance of herpes zoster rash and continued for 7 to 21 days. In one RCT of famciclovir (500 mg initiated within 72 hours of herpes zoster diagnosis and continued for 7 days) involving 186 patients, treatment failed to reduce the overall incidence of PHN but reduced the duration of the disease by a median of 2 months. The seven studies of oral steroids evaluated were too heterogeneous for pooled data analysis. The two studies of steroid use that were the most recently published when the review took place demonstrated a short-term benefit in reducing herpes zoster pain and improving quality of life but offered no evidence of preventing PHN or reducing its severity or duration.
Ahmed compared percutaneous electrical nerve stimulation to famciclovir in a RCT in 50 patients and reported, without detailing the statistical analyses, that treatment with famciclovir reduced the risk of developing PHN and the severity of pain at 3 and 6 months (99).

Cellular immunity plays a more important role than does humoral immunity in fighting both primary infection with VZV and in preventing reactivation. Patients who had a primary VZV infection but have not subsequently been in close contact with children suffering primary infections do not experience the natural boosting of immunity that can occur through this repeated exposure (100). Several investigators have shown that administration of live attenuated varicella Oka strain vaccine boosts cell-mediated immunity to VZV in the elderly (101–103), and it is hoped that the routine vaccination of high-risk patient groups may ultimately prevent PHN. An investigation is ongoing to determine if reexposure to VZV via live vaccine administration in healthy adults over age 60 years can reduce the incidence and severity of PHN (104).

**TREATMENT RECOMMENDATIONS**

Prompt treatment of herpes zoster outbreaks can lessen the associated acute pain and diminish the likelihood of developing PHN. If nonprescription analgesics do not work, consideration should be given to opioids and tricyclic antidepressants for symptomatic relief during the acute zoster episode. Treatment with antiviral medications and steroid medications should be considered on an individual basis. Generally, patients less than 50 years of age who have mild symptoms and are not immunocompromised do not require drug therapy unless the ophthalmic area is involved. Table 1 summarizes the recommendations for specific patient populations, published as the result of a National Institutes of Health Clinical Staff Conference (105). Some patients with extreme pain from an acute outbreak will experience dramatic relief with epidural catheter placement and infusion of local anesthetics or opioids; however, this treatment carries the risk of epidural abscess with prolonged use.

Treatment for established PHN should begin with medications that have established and favorable efficacy and safety profiles; however, a proportion of patients will experience pain that is refractory to both initial and subsequent therapies. A strategy for the treatment of patients with PHN is shown in Figure 1. Lidocaine patches seem to be very safe and are effective for many patients. Patients with marked allodynia without sensory loss on examination may represent a subset with irritable nociceptors and may be the most likely to benefit from lidocaine patches. Capsaicin can desensitize nociceptors, but the burning pain associated with its application can limit its utility.

In addition to lidocaine patches, amitriptyline and gabapentin should be considered first-line treatment, because these drugs have been shown to be effective in multiple RCTs. The NNT for amitriptyline and gabapentin is similar; however, the NNH is lower for amitriptyline. This means

### Table 1.
**Therapy for Zoster Infections**

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<tr>
<th>Patient Group</th>
<th>Treatment Options*</th>
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<tbody>
<tr>
<td>Zoster</td>
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<tr>
<td>Immunocompetent persons</td>
<td></td>
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<tr>
<td>Age &lt;50 years with mild pain</td>
<td>Symptomatic care only</td>
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<tr>
<td>With ophthalmic rash</td>
<td>Oral famciclovir, valacyclovir, or acyclovir for 7 days; ophthalmic assessment</td>
</tr>
<tr>
<td>Age ≥50 years or moderate to severe pain</td>
<td>Oral famciclovir, valacyclovir, or acyclovir for 7 days; consider corticosteroids†</td>
</tr>
<tr>
<td>Immunocompromised persons</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid therapy, continuous or intermittent high dose</td>
<td>Oral famciclovir, valacyclovir, or acyclovir for 7 days</td>
</tr>
<tr>
<td>Low-dose daily cytotoxic drug use†</td>
<td>Oral famciclovir, valacyclovir, or acyclovir for 7 days</td>
</tr>
<tr>
<td>HIV-infected</td>
<td>Oral famciclovir, valacyclovir, or acyclovir for 7–10 days</td>
</tr>
<tr>
<td>Hematologic or solid-organ malignant conditions or</td>
<td>Intravenous acyclovir or oral valacyclovir or famciclovir for 7–10 days</td>
</tr>
<tr>
<td>transplant recipient</td>
<td></td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>Intravenous acyclovir for 10 days</td>
</tr>
<tr>
<td>Acyclovir-resistant lesions</td>
<td>Intravenous foscamet§ for 14 days or longer (until healing)</td>
</tr>
</tbody>
</table>

*Standard dosages are oral acyclovir, 20 mg/kg five times daily for children or 800 mg five times daily for adults; intravenous acyclovir, 500 mg/m² every 8 hours for children or 10 mg/kg every 8 hours for adults; oral valacyclovir, 1000 mg three times per day; oral famciclovir, 500 mg three times per day; intravenous foscamet, 40 mg/kg every 8 hours.
†Oral prednisone, 30 mg twice per day for 7 days, 15 mg twice per day for 7 days, and 7.5 mg twice per day for 7 days.
‡Examples include daily oral cyclophosphamide, methotrexate, azathioprine, and 6-mercaptopurine.
§Not approved by the Food and Drug Administration for this indication.

that amitriptyline will be effective more often but that gabapentin is better tolerated. Although a greater number of studies have established the efficacy of amitriptyline, strong consideration should be given to nortriptyline, because evidence suggests that it may be as effective and better tolerated. It is not known whether these drugs work synergistically or additively. OxyContin and other opioid medications with long half-lives are useful therapies for patients who do not respond to tricyclic antidepressants or antiepileptics. Opiate medications are not selected initially despite their reasonable efficacy because of their side effect profile and potential for physiologic dependence.

Depression is common among patients with chronic pain, and referral for psychiatric consultation can be crucial for PHN patients who have signs and symptoms of mood disturbance. Even those who are free of overt depression and anxiety can learn behavioral strategies to ameliorate refractory pain. Detectable mood disorders should be treated concurrently as efforts to reduce pain continue.

When pain persists despite treatment with lidocaine patches, tricyclic antidepressants, antiseizure drugs, and opioids, the physician is left with treatment options that have less or no established efficacy. Mexiletine can be tried for patients who respond to intravenous lidocaine infusion; however,
potentially serious arrhythmias can occur. Regional anesthetic blocks seem to provide transient analgesia only, but, as in acute zoster, they may occasionally be useful for patients with intolerable pain. Intrathecal steroid injections seem to be promising, but additional studies are needed to determine the safety and efficacy of this treatment for PHN. The role of invasive treatment strategies, such as spinal cord stimulation and neuroablative procedures, also needs to be investigated carefully in future studies.

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REFERENCES


