Postherpetic Neuralgia: An Overview of the Pathophysiology, Presentation, and Management

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Postherpetic neuralgia (PHN) presents itself as a frustrating and fascinating subject within the realm of neuropathic pain. With herpes zoster affecting roughly 3.4 per 1,000 people, and 0.49 per 1,000 people developing PHN annually,¹ the subject continues to be a prevalent dilemma in want of further study.

Acute herpes zoster can recur with activation of the varicella zoster virus (VZV) that has laid dormant in the sensory ganglia.² VZV is initially transmitted via direct contact with or inhalation of aerosolized droplets. In the United States alone, 90% of people are susceptible to the reactivation of the VZV that they harbor.³ Furthermore, there is approximately a 10% to 20% lifetime risk for herpes zoster reactivation.⁴

PHN is preceded by the characteristic neuropathic dermatomal pain and rash (Figure 1), although there have been instances of PHN without this prodrome (as in zoster sine herpete, where diagnosis is confirmed with serologic studies).⁵⁻⁷

A commonly used definition of delineating PHN is suggested by Dworkin as a “significant pain or abnormal sensation 120 days or more after the presence of the initial rash.”⁸ It generally affects the thoracic dermatomes, although cervical and thoracic dermatomes also
may be affected; however, in 23% of the cases, the ophthalmic division of the trigeminal nerve is affected.\(^9\)\(^-\)\(^{11}\)

Risk factors for developing PHN after a herpes zoster infection include older age, immunosuppression, female gender, greater acute pain and dermatomal injury, and severe prodrome.\(^4\)\(^-\)\(^{12}\)\(^-\)\(^{13}\) An incidence of greater than 20% is associated with those over age 50 and approximately a 35% risk in those over 80, whereas there is only about a 2% risk in those under the age of 50.\(^2\) Elderly individuals tend to have greater dermatomal eruptions and nerve damage that can be associated with their decreasing cell-mediated immunity.\(^12\)\(^-\)\(^{14}\)

PHN has profound effects on the quality of life of those affected. In a Medline search that looked at studies surveying people affected by PHN, symptoms other than pain that were shown to be associated with the disease included insomnia, depression, fatigue, loss of appetite with subsequent weight loss, and cognitive impairment.\(^15\)\(^,\)\(^{16}\) In one particular study, 64% of 261 participants reported sleep disturbances; 58% reported negative affects regarding enjoyment of life; and 53% said their general activities were negatively affected.\(^16\)

The pathophysiology behind PHN is a neuronal injury that affects both the peripheral and central components of the nervous system (Figures 2 and 3). This injury causes peripheral neurons to generate spontaneous discharges, while also lowering the threshold for action potentials that generate disproportionate pain, often with nonpainful stimuli.\(^10\) Skin biopsies taken in studies of patients with PHN showed severe loss of epidermal free nerve endings in the affected area\(^9\)\(^,\)\(^{17}\), however, reinervation is not required for pain resolution.\(^17\)

At a cellular level, evidence shows an increase in the number of voltage-gated sodium channels,\(^18\) potassium voltage-gated channel alterations, and upregulation of receptors associated with pain such as transient receptor potential vanilloid 1 (TPRV1).\(^19\) These changes are associated with spontaneous and provoked pain due to a lowered threshold for action potentials. TPRV1 has been studied as a nonselective calcium channel with high calcium permeability that is expressed at the terminal endings of peripheral small-diameter sensory neurons. Thus, inhibition of the TPRV1 receptor may prevent the action potential at the peripheral neurons that lead to pain transmission.\(^20\) There also is evidence of loss of GABAergic inhibitory interneurons at the dorsal horn, as well as loss of descending inhibition.\(^19\)

In addition to sensory neuron damage, motor deficiency can occur from inflammation affecting the anterior horn of the spinal cord.\(^6\)\(^,\)\(^{21}\)

PHN has further been divided into 2 clinical patterns: irritable nociceptor and deafferentation.\(^22\) Irritable nociceptor presents itself as severe allodynia with minimal if any sensory loss, which correlates with C-fiber activity. C-nociceptors normally are only stimulated by noxious stimuli; however, with the phenotypic changes described above (such as that seen in PHN), they become sensitized, lower their threshold for activation, and increase their discharge magnitude. The clinical outcome is peripheral nervous system-mediated allodynia.

Deafferentation is associated with sensory loss and allodynia at the area of scarring. The deafferentation results in dorsal horn reorganization. The sensitized C fibers that are associated with the peripheral pain diminish in quantity with deafferentation. This leads to sprouting of Aβ fibers (large-diameter fibers that respond to mechanical stimuli such as touch and pressure) that ultimately causes them to make connections with the spinothalamic tracts of the spinal cord that are normally synapsing with the C fibers to transmit pain.\(^22\) The clinical outcome of this reorganization due to C-fiber degeneration and resultant rewiring is that touch and pressure types of peripheral stimuli now cross-talk with pain-transmitting spinothalamic tracts in the spinal cord, producing allodynia mediated by the central nervous system. Central sensitization also plays a prominent role in PHN because the insulating injury leads to an overall augmentation in the excitability of the spinal cord neuron, which in general suggests that any input from nociceptors will generate an enhanced response.\(^22\)

Prevention and Treatment

Prevention and treatment are important topics in PHN, although some debate lies within both areas (Table). Vaccines increase cell-mediated immunity and therefore can decrease the incidence and severity of the herpes zoster infection, which can decrease the incidence and severity of PHN. Since the adoption of universal chicken pox vaccination in the United States in 1995, there has been a decrease in VZV infections by 90% to 95% in children aged 1 to 9 years.\(^14\) In 2006, the Centers for Disease Control and Prevention recommended the shingles vaccine in those over age 60 because the risk for developing PHN increases with advancing age.\(^14\)

Within the first 72 hours of acute herpes zoster onset,
Antivirals can decrease the intensity and duration of PHN. The reasoning would be that early antiviral treatment decreases neural damage from the herpes zoster infection. Acyclovir (Zovirax, BTA Pharmaceuticals), famciclovir (Famvir, Novartis), and valacyclovir (Valtrex, GlaxoSmithKline) all have been shown to speed recovery from PHN. Specifically, oral acyclovir has been shown to increase the rate of resolution of PHN pain in 81% of patients compared with placebo. Therefore, it reasonably can be expected that these patients would experience a corresponding reduction in the intensity and duration of PHN. Amitriptyline initiated early, especially in those at high risk for PHN, also has been shown to decrease the severity of PHN.

Although various PHN treatment classifications exist, dividing treatment options into first-, second-, and third-line agents may appear to be useful, but ultimately may prove to be overly simplistic. The authors recommend that in order to decide on the initial analgesic plan and the appropriate follow-up interval, components such as the following should be considered:

- Pain severity,
- Extent of pain’s impact on the patient’s physical and psychosocial function,
- Degree of patient anxiety and depression,
- Side effects and end-organ effect of the analgesics being considered,
- Labor of analgesic titration to effect, and
- Ease of daily analgesic use.

Other analgesic considerations include topical agents that target the peripheral nervous system versus systemic agents, use of monotherapy versus combination pharmacotherapy, and potential for drug-drug interaction between analgesics and other medications that the patient consumes on a daily basis.

Furthermore, many patients with PHN already have a large medical disease burden and corresponding oral pharmacotherapy that would be further complicated with a purely oral neuropathic analgesic treatment plan. Ultimately, pain severity and its physical and psychological impacts determine use of monotherapy versus combination pharmacotherapy, potential use of

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**Figure 2. Examples of peripheral versus central sensitization.**

interventions, and patient follow-up time frame.

For example, there are many patients with PHN who will be simply bothered by their dysesthetic or pruritic symptoms that are not overly painful or crippling to them. Such patients would benefit from monotherapy with agents such as a 5% lidocaine patch, every-3-month application of an 8% capsaicin patch, low-dose twice- or thrice-daily pregabalin or gabapentin, or a once-daily low-dose tricyclic antidepressant (TCA) such as nortriptyline.

For more formidable pain presentations, a combination analgesic plan should be considered. Interventional techniques that are not the focus of this review also can be useful in bringing the crippling pain under prompt control. Other options include transcutaneous electrical nerve stimulation (TENS), botulinum toxin injection, and acupuncture, which largely can serve as adjuncts to the pharmacologic plan.

There is evidence that combination, multimechanistic therapy that covers the peripheral and central nervous systems increases the overall therapeutic effect.28,29

It is important to emphasize that the topical PHN analgesics, such as 5% lidocaine or 8% capsaicin patches, can have major advantages over oral systemic medications because they provide clinically meaningful pain relief without laborious analgesic titration, while having much improved side-effect and end-organ safety profiles. It is further our opinion that a topical option, by not adding additional pill counts to the patient’s daily regimen, improves the patient’s daily medication routine and overall adherence to oral treatment.

The 5% lidocaine patch (Lidoderm, Endo Pharmaceuticals) mechanism of action (MOA) is at the voltage-gated sodium channel to prevent peripheral action potentials. Continued use of a 5% lidocaine patch over a 2-week period produces peripheral desensitization and, likely over that same time frame, central desensitization as well. The 5% lidocaine patch produces pain relief over 2 weeks in 84% of patients with PHN, and has a favorable efficacy, tolerability, and side-effect profile, thus making it an appropriate choice for first-line monotherapy or as part of the first-line multimechanistic analgesic plan of care. In a double-blind, randomized study of 46 patients, the lidocaine patch was associated with statistically significant decreases in pain scores in those patients affected by PHN relative to a vehicle patch. A further assumption can be made that the physical barrier that the 5% lidocaine patch provides between the skin and outside stimulus adds to the analgesic effect.30

Up to 3 of the 5% lidocaine patches should be prescribed to cover the painful dermatome for 12 hours per day. It is important to cover the involved dermatome thoroughly to maximize peripheral deafferentation and the potential reduction of central sensitization. At the maximum dose of 3 of these patches applied for 12 hours per day, the analgesic is associated with excellent tolerability and end-organ safety profile. Local anesthetic advantage is production of clean analgesia that allows these patients to return to the normalcy of life.31 It is important to keep in mind that although the initial analgesic effect occurs within hours of the first 5% lidocaine patch application, the best effects are realized after 2 weeks of treatment. Titration is unnecessary with the 5% lidocaine patch. The most common side effect reported is a skin rash that often is transient.

Calcium channel ligands such as gabapentin (Neurontin, Pfizer) and pregabalin (Lyrica, Pfizer) are shown to be superior to placebo in reducing pain by decreasing the calcium influx into the nerve endings and thereby diminishing the quantity of excitatory neurotransmitters released at the nerve terminal.28,32,33 In multicenter, randomized placebo-controlled trials, pregabalin produced a greater decrease in pain and improvements in sleep compared with placebo.

Pregabalin has more linear and predictable absorption with dosing increases as well as twice-daily dosing convenience compared with gabapentin. The initial daily dose of pregabalin is 100 to 150 mg, given in 2 to 3 divided doses, with a maximum dose of 600 mg. Although side effects of these analgesics can be dose-limiting, often slowing down the titration by decreasing the dose or increasing the dose interval can allow adjustments to the analgesic effect to proceed. The more common side effects reported with pregabalin are dizziness, sedation, weight gain, peripheral edema, blurred vision, diplopia, headache, and ataxia. The side-effect incidence and intensity are dose-dependent.

TCAs are effective in PHN by exerting analgesic effects as well as targeting the depression that is commonly associated with the disease. The MOA of TCAs is that of blocking norepinephrine and serotonin uptake, sodium channels, and working as an N-methyl-D-aspartic acid (NMDA) antagonist (as pain also is transmitted via NMDA receptors in the central nervous system).27,29 TCAs have largely fallen out of the commonly used armamentarium of many clinicians. This is unfortunate because they essentially use the same mechanism to achieve analgesia as analgesics such as duloxetine (Cymbalta, Eli Lilly) with a comparable tolerability and safety profile at a great cost savings. TCAs such as nortriptyline can be part of the analgesic plan when sleep is interrupted and mood needs to be addressed pharmacologically or anticonvulsant dosing is limited by side effects. Nortriptyline is started at 10 mg at bedtime and is titrated weekly to effect or up to a dose of 30 to 50 mg at bedtime.

Opioids exert their effects on μ receptors to produce analgesia. Tramadol acts on the Q receptors while also limiting serotonin and norepinephrine reuptake at synapses. Tramadol has a lesser risk for abuse than the pure opioid compounds.34 The side-effect profile of the opioid group is poor and may explain the results of one study in which there was no difference in pain reduction between TCAs and opioids, although there was a greater number of dropouts in the opioid group. There often is a need to titrate opioids to analgesic effect and often this titration is limited by nuisance or function-limiting side effects, as well as intolerable side effects.
The 8% capsaicin patch (Qutenza, NeurogesX) is a newly available medication for treatment of the neuropathic pain of PHN. Its MOA is initial activation of the TRPV1 on nociceptors that produces pain and erythema. The consequence of this primary afferent depolarization is partial nociceptor inactivation and corresponding analgesia. In 2 double-blind, randomized studies of 402 and 416 subjects with mean PHN duration of approximately 3 to 4 years, 44% and 47% of patients, respectively, experienced 30% or greater pain reduction. This was a statistically significant improvement over the response to 0.04% capsaicin patch that served as an active control.

The 8% capsaicin patch is designed to be applied over the painful area for 60 minutes every 90 days after appropriate local anesthetic application to the skin. Except for the local application-site pain, related blood pressure elevation, and transient skin reaction, the 8% capsaicin patch is generally well tolerated and allows up to 3 months of clinical improvement with potentially less reliance on oral analgesics. An adequate number of patches needs to be prescribed to cover the painful dermatome, not to exceed 4 patches. The application-site pain increases proportionately with the number of patches applied. Therefore, adequate anesthetizing of the skin is critical to a successful 60-minute application. There are no end-organ effects of or contraindications to capsaicin.

Because of its recent availability, the role of the 8% capsaicin patch within the treatment spectrum is not well established. However, given its safety, procedural simplicity, and potential to decrease opioid and anticonvulsant use, it can be offered to patients to potentially reduce oral analgesic consumption, related side effects, and end-organ effects, as well as improve treatment adherence.

Interventional procedures often are limited to refractory disease, analgesic failures, or circumstances where prompt relief is psychologically necessary. They also can be used to reduce reliance on analgesics.

There is inadequate evidence to support the use of TENS to treat PHN. TENS works by stimulating the cutaneous nerve fibers with mild current, with adjustments in frequency, intensity, and pulse durations.
Spinal cord stimulators (SCS) are dependent on anatomically intact pathways and work by placing a lead in the epidural space that is then connected to a pulse generator. Its MOA is activation of spinal opioid receptors and decreases in afferent neural transmission.\(^{28}\) Descending inhibition also may be involved in the MOA of SCS.\(^{39}\)

Botulinum toxin is a neurotoxic protein that has been used largely to treat dystonias and refractory headaches. Although larger studies are needed to advocate its use, one double-blind study of 60 patients showed improvements in PHN pain. The proposed MOA is inhibition of neurotransmitter release at the peripheral nerves.\(^{40,41}\) Although strong evidence is lacking and clearly controversial, spinal nerve injections with local anesthetic and steroids initiated during acute herpes zoster is a possible method for prevention of PHN. The mechanism may be that decreasing the pain and inflammation early on during acute herpes zoster can reduce the risk for development of PHN because severity and duration of neural inflammation is a risk factor for PHN development.\(^{42}\)

Finally, acupuncture is supported by some case reports showing clinical efficacy in the treatment of PHN.\(^{43}\) However, in the study conducted by Lewith comparing acupuncture with placebo in PHN, there was no difference in pain relief.\(^{44}\) Its purported MOA is promotion of endorphin release by stimulation of peripheral nerves.\(^{45}\)

### Treatment Strategy Recommendations

When weighing the many treatment options for PHN, analgesic goals include maximizing efficacy, patient function, tolerability, end-organ safety, patient convenience, and treatment adherence.

A common discussion is whether topical analgesics should take precedence over systemic medications for mild to moderate cases of PHN. Furthermore, do topical agents add analgesic value for patients with severe PHN who already are being treated with one or more oral analgesics?

The authors’ opinion is that topical analgesics always should be trialed as part of the initial plan that is comprised of either a single analgesic or multiple analgesics. The main reason for this strategy is that topical analgesics treat the peripheral nervous system, which is not treated by anticonvulsants, opioids, and antidepressants. Addressing the peripheral nervous system pain allows reduction of peripherally mediated central pain and consequent potential reduction of central pain. This overall improvement provides excellent side-effect and end-organ safety and practical advantages to the patient.

Maximizing the topical analgesic benefit has the potential to simplify and reduce systemic analgesic use and its associated titration, side effects, and complexity. This strategy is particularly helpful in elderly populations, which data show is the group most likely to be affected by PHN. Side effects are more likely not tolerated within this population, as well as in those patients who are analgesic-naïve or -sensitive.

Systemic oral agents can be prescribed with topical analgesics as part of the initial analgesic plan or subsequently during a follow-up visit in several weeks. Multimechanistic treatments have been found to be effective, and the proposed multimechanistic method of treatment with solely topical agents or topical agents in combination with systemic agents addresses the injured peripheral and central pathways that are producing the neuropathic pain of PHN.

PHN is a clinically significant disease that extends its effects beyond just pain and encroaches on the individual’s quality of life and psychosocial health. Pain is brought on by the initial or recurrent injury to the neurons from the acute herpes zoster infection, leading to increased peripheral and central sensitization. Treatment options are numerous and multimechanistic, and multimodal approaches have been found to be beneficial. The treatment plan should aim to maximize physical and psychosocial function of patients by using topical agents alone or in balance with systemic agents to optimize clinical outcomes.

### Table. Overview of Pharmacologic Treatments for Postherpetic Neuralgia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Lidocaine 5% patch (Lidoderm, Endo)</td>
<td>Voltage-gated sodium channel antagonist</td>
<td>Up to 3 patches for 12 h/d; no need to titrate</td>
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<tr>
<td>Capsaicin 8% patch (Qutenza, NeurogesX)</td>
<td>Initially activates TRPV1, then renders it inactive</td>
<td>Up to 4 patches for 1 h every 3 months or longer</td>
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<tr>
<td>Tricyclic antidepressants</td>
<td>Blocks norepinephrine and serotonin</td>
<td>Varies with different TCAs; need to titrate</td>
</tr>
<tr>
<td>Calcium channel ligands</td>
<td>Decreases calcium influx into the nerve ending, diminishing the quantity of excitatory neurotransmitters released at the nerve terminal</td>
<td>gabapentin: titration up to 3,600 mg/d; pregabalin: titration up to 600 mg/d;</td>
</tr>
<tr>
<td>Opioids</td>
<td>Affects µ receptors; acts to increase inhibition of norepinephrine and serotonin</td>
<td>Varies; need to titrate; high side-effect profile</td>
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References
20. Premkumar LS. Targeting TRPV1 as an alternative approach to narcotic analgesics to treat chronic pain conditions. AAPS J. 2010;12(3):361-370.
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