Neuropathic Pain of Postherpetic Neuralgia

Overview

Postherpetic neuralgia (PHN) presents itself as a frustrating and fascinating subject within the realm of neuropathic pain. With acute herpes zoster (AHZ) affecting about 1 million patients per year and up to 20% of these patients developing PHN annually,¹ PHN and its clinical management continues to be a prevalent dilemma.
AHZ infection can recur with activation of the varicella zoster virus (VZV) that has been dormant in the sensory ganglia. VZV is initially transmitted via direct contact or inhalation of aerosolized droplets. In the United States alone, 90% of people are susceptible to the reactivation of the VZV that they have harbored since their experience with chickenpox, usually as a child. There is approximately 30% lifetime risk for AHZ reactivation. Of those patients who develop AHZ, 10% to 20% develop PHN.

PHN is preceded by the characteristic neuropathic, dermatomal pain and skin manifestations that can range from a simple rash to a vesicular eruption (Figure 1). There also have been instances of AHZ and PHN without the dermatologic manifestations (ie, zoster sine herpete).

A commonly used definition of PHN is suggested by Dworkin as a “significant pain or abnormal sensation 120 days or more after the presence of the initial rash.” PHN generally affects the thoracic dermatomes, although cervical, trigeminal, and lumbosacral dermatomes may also be affected. The trigeminal nerve most commonly is affected at its V1 ophthalmic division. About 10% to 20% of patients with AHZ develop PHN.

There is controversy in the literature regarding the time frame for establishing the diagnosis of PHN, which ranges from pain upon dermal healing to 6 months after the AHZ lesions have healed. PHN pain often is misdiagnosed and underdiagnosed.

The pathophysiology of neuropathic pain of PHN has both peripheral (PNS) and central nervous system (CNS) components. Therefore, its treatment can be tailored to target the PNS as well as the ascending and descending pathways of the CNS.

The ideal treatment and follow-up regimen takes into account the severity of the patient’s pain, anxiety, depression, and the impact of the pain on physical and psychosocial function. The spectrum of pharmacotherapy ranges from monotherapy for mild pain to a combination of topical agents, opioids, anticonvulsants, and antidepressants for more severe pain presentations.

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Risk factors for developing PHN after an AHZ infection include older age, immunosuppression, female gender, greater acute pain, dermatomal injury, and severe prodrome. PHN incidence of greater than 20% is associated with those older than 50 years of age, and approximately a 35% risk is seen for those older than 80 years of age; there is only approximately a 2% risk for developing PHN in those under 50 years of age. Elderly individuals tend to have greater severity of dermatomal eruptions and nerve damage that can be explained with age-related decrease of cell-mediated immunity.
PHN has profound effects on the quality of life of those affected. In a Medline search that reviewed 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. In one particular study of 261 patients, sleep was affected in 64%, enjoyment of life in 58%, and general activity in 53%.

Pathophysiology

The pathophysiology of PHN is neuronal injury that affects both the peripheral (PNS) and central nervous system (CNS) (Figures 2 and 3). This injury causes peripheral and central neurons to generate spontaneous discharges while also lowering the activation threshold to generate disproportionate pain with nonpainful stimuli. Interestingly, skin biopsies taken in studies of patients with PHN show severe loss of epidermal free nerve endings in the affected areas; reinnervation is not required for pain resolution. At a cellular level, evidence shows an increase in the proportion of subtype of voltage-gated sodium channels, potassium voltage-gated channel alterations, and upregulation of receptors associated with pain such as transient receptor potential vanilloid 1 (TRPV1). These changes are associated with spontaneous and provoked
pain due to a lowered threshold for action potentials. TRPV1 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 TRPV1 receptor may prevent the action potential at the peripheral neurons that lead to pain transmission. There also is evidence of loss of γ-aminobutyric acid inhibitory interneurons at the dorsal horn as well as loss of descending inhibition.

Although there is predilection for involvement of sensory ganglia and nerves, motor deficits may occur from the spread of the infection and inflammation to the anterior horn of the spinal cord. PHN has been subdivided into “irritable nociceptor” and “deafferentation” models. The irritable nociceptor model correlates with C-fiber activity and presents as severe tactile, mechanical, and thermal allodynia with minimal if any sensory loss. C-fiber nociceptors normally are stimulated only by noxious stimuli; however, with the cellular changes described above they become sensitized, lower their threshold for action potentials, and increase their discharge rate and magnitude. The clinical outcome is PNS-mediated spontaneous pain and allodynia.

The deafferentation model is associated with allodynia and sensory loss at the involved dermatomes. The peripheral deafferentation results in dorsal horn reorganization. The sensitized C fibers of the peripheral nerve diminish in quantity with deafferentation, which leads to sprouting of A-β fibers (large-diameter fibers that respond to mechanical stimuli such as touch and pressure). The A-β fiber sprouting ultimately produces connections with the spinothalamic tracts of the spinal cord that were previously synapsing with the C fibers to transmit pain. The clinical outcome of this dorsal horn reorganization due to C fiber degeneration and resultant A-β rewiring is that touch and pressure type of peripheral stimuli now “crosstalk” with pain-transmitting spinothalamic tracts at the spinal cord, producing allodynia mediated by the CNS.

Central sensitization also plays a prominent role in PHN due to the constant barrage of PNS impulses to the spinal cord, as well as the direct viral injury leading to chronic excitability of the second-order neurons. Therefore, normal and excessive input from peripheral nociceptors generates an enhanced central response.

Prevention and Treatment

Vaccines increase cell-mediated immunity and therefore can decrease the incidence and severity of the AHZ, which can decrease the incidence and severity of PHN. Since the adoption of universal chickenpox vaccination in the United States, there has been a decrease in VZV infections by 90% to 95% in children aged 1 to 9 years. In 2006, the Centers for Disease Control and Prevention recommended the shingles vaccine in those older than 60 years due to the risk for developing PHN with advancing age.

Within the first 72 hours of the appearance of herpetic rash, antivirals can decrease the intensity and duration of PHN. This is presumably due to decreased neural damage from the early treatment of the VZV infection. Acyclovir (Zovirax, BTA Pharmaceuticals), famciclovir (Famvir, Novartis), and valacyclovir (Valtrex, GlaxoSmithKline) all have been shown to speed recovery from AHZ. Specifically, oral acyclovir has been shown to increase the rate of resolution of PHN pain in 81% of patients compared with placebo. Therefore, it can be expected that these patients would experience a corresponding reduction in the intensity and duration of PHN that they may experience. Amitriptyline initiated early, especially in those at high risk, 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 proves to be overly simplistic. The author recommends that components such as pain severity, the extent of the pain’s impact on the patient’s physical and psychological function, degree of anxiety and depression, side effects and end-organ effect of the analgesics considered, labor of analgesic titration to effect, and ease of daily analgesic use decide the initial analgesic plan and the appropriate follow-up interval (Table).

Other analgesic considerations include topical agents that target the PNS versus systemic agents, use of monotherapy versus combination pharmacotherapy, and potential for drug–drug interaction between analgesics and other medications that a patient is consuming on a daily basis. Furthermore, many PHN patients already have a large medical disease burden and corresponding oral pharmacotherapy that would be further complicated by a purely oral neuropathic analgesic treatment plan.

Ultimately, the pain severity and its physical and psychological impact determines use of monotherapy versus combination pharmacotherapy, use of opioids, potential use of interventions, and patient follow-up time frame.

For example, there are many PHN patients who will be simply “bothered” by dysesthetic or pruritic symptoms that they do not find to be overly painful or crippling. These patients would benefit from monotherapy with agents such as 5% lidocaine patch; 8% capsaicin patch; low-dose, once-, twice- or thrice-daily pregabalin or gabapentin; or once-daily, low-dose tricyclic antidepressants (TCAs) such as nortriptyline. Furthermore, with the recent availability of once-daily gabapentin, patient acceptance and convenience can be...
enhanced while minimizing the daily pill count the patient consumes.

For more formidable pain presentations, a combination analgesic plan is considered. Interventional techniques can be useful in bringing the crippling pain under prompt control. There is evidence that combination, multimechanistic therapy that covers the PNS and CNS provides the best overall therapeutic effect.28,29

Topical PHN analgesics, such as 5% lidocaine patch (Lidoderm, Endo) or 8% capsaicin patch (Qutenza, NeurogesX) can have major advantages over oral systemic medications. Topical analgesics provide clinically meaningful pain relief while having much improved side-effect and end-organ safety profiles without laborious analgesic titration associated with oral agents. Furthermore, topical options, by not adding additional pill counts to the patient’s daily regimen, improve patients’ daily medication routine and overall adherence to treatment.

The 5% lidocaine patch mechanism of action (MOA) is at the voltage-gated sodium channel, so as to attenuate peripheral nerve action potentials. Continued use of 5% lidocaine patch over a 2-week period produces peripheral desensitization and probable central desensitization. The 5% lidocaine patch produces significant 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 5% lidocaine patch showed statistically significant decreases in pain scores in those affected by PHN relative to a vehicle patch. A further

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**Figure 3. Target pathways of PHN pain.**

NMDA, N-methyl-D-aspartate; PHN, postherpetic neuralgia; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCAs, tricyclic antidepressants

*a* Opioids, tramadol; *b* TCAs, SNRIs, SSRIs; *c* Oxcarbazepine, levetiracetam, lamotrigine; *d* Ketamine, dextromethorphan, memantine, methadone; *e* Carbamazepine, oxcarbazepine, phenytoin, topiramate, lamotrigine; *f* Lidocaine, capsaicin, mexiletine.

assumption can be made that the physical barrier that the 5% lidocaine patch provides between the skin and outside stimuli adds to its analgesic effect.30

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

Calcium channel ligands such as gabapentin (Neurontin, Pfizer; Gralise, Depomed) and pregabalin (Lyrica, Pfizer) are shown to be superior to placebo in reducing pain by decreasing the calcium influx into the nerve endings, thereby diminishing the quantity of excitatory neurotransmitters released at the central nerve terminals.32-35 In multicenter, randomized, placebo-controlled trials, pregabalin produced greater decreases in pain and improvements in sleep when compared with placebo.

Pregabalin exhibits linear and predictable absorption and twice-daily dosing convenience compared with gabapentin. The initial dose of pregabalin is 100 to 150 mg daily, given in 2 to 3 divided doses, with a maximum dose of 600 mg per day. Although the side effects of anticonvulsants can be dose-limiting, slowing down the titration by decreasing the individual dose or increasing the dose interval often allows dose adjustments toward 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 severity are dose-dependent.

Although these are effective and transformative treatments for neuropathic pain, the unfortunate consequence of pregabalin or gabapentin therapy is a complex, burdensome titration regimen often based on thrice-daily dosing. The population suffering from neuropathic PHN is probably least well equipped to deal with such complexity.

Once-daily gabapentin (Gralise, Depomed) was recently approved by the FDA and is a welcome addition to the analgesic armamentarium that can improve patient acceptance due to its daily dosing and favorable side-effect profile. The analgesic efficacy of once-daily gabapentin in PHN has been shown in placebo-controlled trials. Additionally, the data have shown that the incidence of dizziness and somnolence is also markedly reduced relative to similar studies using gabapentin thrice-daily and pregabalin. The reduction of these adverse events with once-daily gabapentin may be

<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 mo or longer</td>
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<tr>
<td>TCAs</td>
<td>Blocks norepinephrine and serotonin</td>
<td>Varies with different TCAs; need to titrate</td>
</tr>
<tr>
<td>Calcium channel ligands (gabapentin [Neurontin, Pfizer]; Gralise, Depomed); pregabalin [Lyrica, Pfizer]</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. Neurontin is dosed tid. Gralise is dosed qHS with the evening meal. Pregabalin: titration up to 600 mg/d on a bid or tid regimen</td>
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<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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bid, twice daily; qHS, nightly at bedtime; TCAs, tricyclic antidepressants; tid, thrice daily; TRPV1, transient receptor potential vanilloid 1
related to nighttime dosing and/or its more gradual rise to peak level when compared with the thrice-daily formulation. Once-daily gabapentin comes as a 30-day titration pack to facilitate dosing and is taken once a day with the evening meal.35

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 reuptake, sodium channels, and working as an N-methyl-D-aspartic acid (NMDA) antagonist (as pain also is transmitted via NMDA receptors in the CNS).8,36 TCAs have largely fallen out of the armamentarium of many clinicians. This is unfortunate because TCAs essentially achieve the same mechanism of 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. For example, nortriptyline, amitriptyline, or doxepin may be started at 10 mg at bedtime and is titrated weekly to effect or up to a dose of 20 to 50 mg at bedtime.

Opioids exert their effects on µ-receptors to produce analgesia. Tramadol acts on the µ-receptors while also limiting serotonin and norepinephrine reuptake at synapses. Tramadol has a lesser risk for abuse than the pure opioid compounds.36 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, whereas there was a greater number of dropouts in the opioid group.36 There often is a need to titrate opioids to analgesic effect, and often this titration is limited by nuisance, function-limiting, or intolerable side effects. Opioids unfortunately are overprescribed and overmanaged at times. Optimal- ly, a low-dose, long-acting opioid formulation as part of the multimechanistic, pharmacologic treatment plan can add analgesic effect and facilitate earlier pain relief. Clinicians have a tendency to hypermanage the opioid category. Low-dose, extended-release formulations can be given once a day or twice a day 8 or 12 hours apart. Titrations ideally occur every 5 to 7 days, and if several titrations are ineffective, consideration should be given to a different opioid compound.

The 8% capsaicin patch is a newly available medication for treatment of neuropathic pain of PHN. Its mechanism of action is initial activation of the TRPV1 receptor on the nociceptive endings that produces pain and erythema. The consequence of this primary afferent depolarization is partial, prolonged C-fiber inactivation and corresponding long-term analgesia.37,38 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 response compared with that seen with 0.04% capsaicin patch, the active control.37

The 8% capsaicin patch is designed to be applied over the painful area for 60 minutes every 90 days, following 60-minute local anesthetic application to the skin. Except for the local pain, related blood pressure elevation, and transient skin reaction, 8% capsaicin patch is generally well tolerated and allows up to 3 months of clinical improvement with potentially less reliance on oral analgesics.37 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 patches applied. Therefore, adequate anesthetizing of the skin is critical to a successful 60-minute capsaicin patch application. There are no end-organ effects or contraindications to capsaicin.

Due to its recent availability, the role of 8% capsaicin patch within the treatment spectrum is not well established. However, given its safety, procedural simplicity, and potential to decrease systemic analgesic use, it can be offered to patients to potentially reduce their 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.

Although strong evidence is lacking and clearly controversial, spinal nerve injections with local anesthetic and steroids initiated during AHZ is a possible method for prevention of PHN. The postulated mechanism for this procedure is that decreasing the pain and inflammation early on during AHZ can reduce the risk for development of PHN, because severity and duration of neural inflammation is a risk factor for PHN development.39

Spinal cord stimulation (SCS) efficacy is dependent on anatomically intact pathways. Their postulated MOA is the activation of spinal opioid receptors and/or decreasing afferent neural transmission.40 Descending inhibition also may be involved in the MOA of SCS.40 The overall experience in treatment of PHN with SCS is limited.

Other options may include transcutaneous electrical nerve stimulation (TENS), botulinum toxin injection, and acupuncture, all of which largely can serve as adjuncts to the pharmacologic plan. There is inadequate evidence to support the use of TENS to treat PHN. TENS works by stimulating the cutaneous nerve fibers with mild current and allows adjustments to frequency, intensity, and pulse duration.41,42

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 the inhibition of neurotransmitter release at the peripheral nerves.

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

**Summary and Treatment Recommendations**

There is a 30% lifetime risk for VZV reactivation and AHZ development. The extent of nerve damage sustained by the PNS and CNS may result in chronic pain beyond the expected healing period. There is controversy in the literature regarding the appropriate time frame for diagnosing PHN; the acceptable time frame is 1 to 6 months after the resolution of the skin lesions. The diagnostic time frame controversy and expected resolution of the symptoms in many patients should not delay the treatment of the neuropathic pain.

The involvement of the PNS and CNS in pain generation needs to be considered in the treatment strategy. When weighing the many treatment options for PHN, analgesic goals include optimization of efficacy, patient function, tolerability, end-organ safety, patient convenience, and treatment adherence. Topical agents and once-daily formulations of opioids and gabapentin can provide efficacy, patient convenience, and favorable tolerability profiles.

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 pain who already are being treated with one or more oral analgesics?

Topical analgesics can be considered as a component of the initial multimodal treatment plan as well as part of the combination analgesic plan that incorporates systemic agents. Use of topical analgesics allows treatment of the PNS that anticonvulsants, opioids, and antidepressants do not address. Treating the PNS pain allows reduction of peripherally mediated central pain and putative reduction of central pain. This overall improvement with topical analgesics is provided with excellent side-effect profiles and end-organ safety, as well as practical advantages for the patient. Furthermore, maximizing topical analgesic benefit has the potential to simplify and reduce systemic analgesic use and its associated titration, side effects, and complexity.

When the decision is made to treat the patient with systemic agents, one should keep in mind that adherence suffers with multidrug, complex dosing. Therefore, given that most PHN patients suffer from constant pain, agents that allow once- or twice-daily dosing can simplify the patient’s daily medication burden.

This strategy is particularly helpful in elderly populations, given that the elderly are most likely to be affected by PHN. Side effects are poorly tolerated in the elderly population, as well as in those patients who are analgesic naïve or sensitive. Oral agents are prescribed with the topical analgesic as part of the initial analgesic plan or subsequently during a follow-up visit.

PHN is an often underdiagnosed and misdiagnosed 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 AHZ infection, leading to increased peripheral and central sensitization. Treatment options are numerous, and multimechanistic and multimodal approaches are most beneficial, providing quality pain relief that allows patients to maximize their physical and psychosocial function.

**References**


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