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Post-herpetic Neuralgia: a Review

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Abstract Post-herpetic neuralgia (PHN) is a chronic neuropathic pain condition that persists 3 months or more following an outbreak of shingles. Shingles, also known as acute herpes zoster, is associated with the reactivation of the dormant varicella zoster virus in an individual who has experienced chicken pox. PHN is associated with persistent and often refractory neuropathic pain. Patients may experience multiple types of pain including a constant deep, aching, or burning pain; a paroxysmal, lancinating pain; hyperalgesia (painful stimuli are more painful than expected); and allodynia (pain associated with typically non-painful stimuli). The pharmacological treatment of PHN may include a variety of medications including alpha-2 delta ligands (gabapentin and pregabalin), other anticonvulsants (carbamazepine), tricyclic antidepressants (amitriptyline, nortriptyline, doxepin), topical analgesics (5 % lidocaine patch, capsaicin) tramadol, or other opioids. The considerable side effect profiles of the commonly used oral medications often limit their practical use, and a combination of both topical and systemic agents may be required for optimal outcomes. Physicians and other treatment providers must tailor treatment based on the response of individual patients.

Keywords Post-herpetic neuralgia · Varicella zoster · Tricyclic antidepressants · Gabapentin · Pregabalin · Chronic pain · Analgesia

This article is part of the Topical Collection on *Other Pain*

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Introduction

The varicella zoster virus (VZV), the same virus that causes chicken pox in children, is a neurotropic herpes virus that lays dormant in the dorsal root ganglion and can reactivate during later adulthood, resulting in acute herpes zoster (AHZ), also known as shingles [1, 2, 3••]. More than 95 % of the young adults of North America manifest seropositivity for antibodies to the varicella zoster virus and are therefore at risk for developing this condition [1, 3••]. After the initial varicella zoster infection, the virus persists in the ganglia of the sensory cranial nerves and spinal dorsal root ganglia without triggering symptoms for many years [2, 3••]. However, with the decline of cell-mediated immunity consequent to stress, illness, medications, aging, or idiopathic causes [2, 4, 5], the risk of AHZ increases dramatically causing the reactivation of the dormant virus in the dorsal root or cranial ganglion, resulting in a unilateral, localized painful blistering skin rash within a single dermatome [1, 2, 3••]. Eruption of AHZ in multiple dermatomes may occur in immunocompromised patients, indicating potentially life-threatening disseminated AHZ [6–8].

It is estimated that the annual incidence of acute herpes zoster is 3.4 cases per 1000 persons, rising significantly from the age of 50 years to approximately 11 cases per 1000 by the ninth decade of life [3••, 9]. Similarly, the Olmsted County Study found that the incidence of AHZ was 3.6 cases per 1000 person-years, but was low in individuals aged 20–29 years

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and spiked to 7.1 cases per 1000 person-years in the seventh decade of life and reached 12.0 cases per 1000 person-years in individuals aged 80 years old [10].

AHZ is characterized by an acute pain of a 2- to 4-week duration that precedes the onset of rash by 7 to 10 days [11, 12]. The distinctive rash presents as a red maculopapular eruption that evolves into vesicles, pustules, and crusts [2]. Although the symptoms of AHZ typically resolve within 2 to 4 weeks, approximately 10 % of patients develop postherpetic neuralgia (PHN) which is defined as pain persisting more than 3 months after the onset of the rash in the same affected area [10, 11, 13]. PHN is the most frequent chronic complication of herpes zoster and the most common neuropathic pain resulting from infection [3••]. It is an exceptionally complex drug-resistant neuropathic pain that results from changes in peripheral and central nervous system somatosensory processing [2, 14]. Most patients with PHN describe three types of pain: a constant deep, aching, or burning pain; a paroxysmal, lancinating pain; and allodynia. Some patients also complain that itching may be more irritating than the pain itself [15–17].

Post-herpetic neuralgia causes considerable suffering and results in a health-care burden at both the individual and societal levels. Patients with PHN suffer from reduced quality of life, physical functioning, and psychological well-being [18, 19]. Despite the potentially debilitating nature of this disorder, PHN tends to be underdiagnosed and inadequately managed, especially in primary care [20].

Considering the wide impact this disorder has on the general population, this important neurological complication should be appropriately appreciated. Managing control over the pain associated with PHN has proven to be a struggle for physicians related to the condition's ability to linger indeterminately. A reduction of pain by 30 % is considered clinically significant, and reaching this goal in PHN patients is usually accomplished only half of the time. When successful, providers appear to use a myriad of treatment algorithms consisting of both on- and off-label pharmaceuticals. The remainder of this paper aims to aggregate the various treatment options for PHN, to identify new developments in the field, and to outline a focused recommendation for providing care to the affected patient.

Pathophysiology

The pathophysiology of PHN involves disturbances within the central and peripheral nervous systems (PNS). During the AHZ episode, the dormant virus becomes activated, replicates, and propagates along the affected nerve, ultimately triggering an inflammatory immune response capable of damaging peripheral and central neurons [11]. Newly synthesized viral particles undergo axonal transport along the central and distal axons of all types of sensory neurons. This causes generalized necrosis and cell death in the skin (and sometimes in the CNS) and within the nerve, root, and ganglion [21]. Damaged, the peripheral nerves lose the ability to inhibit nociception pain signals. This lowers the threshold for nociceptive pain activation and produces spontaneous ectopic discharges. The end result generates disproportionate pain with non-painful stimuli, a phenomenon known as peripheral sensitization [22].

HZV-induced nerve inflammation also impairs the descending inhibitory pain pathways, secondary to compromise of the dorsal horns, and leads to central sensitization [22]. This phenomenon plays an important role in PHN due to the constant transmission of aberrant 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 [3••]. As a result, peripheral neurons' death and central nervous system changes induce an abnormal reorganization of the pain stimuli transmission system and a disorganized innervation pattern that creates the spontaneous pain of PHN [3••, 23].

At the cellular level, PHN upregulates the receptors typically associated with pain, such as the transient receptor potential vanilloid 1 (TRPV1) [24], as well as an increase in the proportion of voltage-gated sodium channels and potassium voltage-gated channels [25]. There is also evidence of loss of γ-aminobutyric acid inhibitory interneurons at the dorsal horn in addition to loss of descending inhibition [24]. Watson et al. compared autopsy tissue from patients with and without PHN after shingles and found that patients with PHN had marked degeneration of their spinal cord dorsal horns [26]. However, it remains unknown whether this dorsal horn atrophy is caused by direct infection of the spinal cord or by trans-synaptic degeneration [27].

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 [28]. Motor neuron axons or cell bodies often undergo degeneration due to the spread of inflammatory cells and molecules from nearby infected somatosensory cells, and some patients develop signs of motor compromise as well as pain [29, 30].

PHN has been subdivided into irritable nociceptor and deafferentation models [31]. The irritable nociceptor model presents as severe mechanical, thermal, and tactile allodynia with minimal if any sensory loss and correlates with C fiber activity. Normally, C-fiber nociceptors are stimulated by noxious stimuli. However, with the molecular changes previously described, the C fibers become sensitized, lower their threshold for action potentials, and increase their discharge rate and magnitude, resulting in the PNS-mediated spontaneous pain and allodynia [31].

The deafferentation model is associated with allodynia and sensory loss at the involved dermatomes resulting in dorsal horn reorganization and a diminished number of C fibers in the affected zone. Interestingly, skin biopsies taken in studies of patients with PHN show severe loss of epidermal free nerve endings in the affected areas [32]. This phenomenon leads to sprouting of A-β fibers (large-diameter fibers that respond to mechanical stimuli such as touch and pressure) and ultimately produces connections with the spinothalamic tracts that previously transmitted pain via synapses with C fibers. This dorsal horn reorganization interconnects spinothalamic tracts and pressure-type peripheral stimuli, producing CNS-mediated allodynia [33].

Treatment

Special considerations must be accounted for prior to initiating treatment in PHN patients. The typical PHN patient takes on average 5 or more drugs pertaining to age-related issues. The bulk of these medications consist of blood pressure and lipid-lowering agents, and a significant number of patients will succumb to these medication side effect profiles (usually presenting with dizziness and drowsiness) [34]. These already sensitive patients may continue to experience synergistic side effects when adding additional PHN pharmaceuticals. The aim of the physician should be to prevent these unwanted issues from ever surfacing by performing a thorough baseline neurological and physical exam—making sure to assess balance, gait, and orthostatics [35••]. In addition, ordering pretreatment labs will help to characterize any potential cardiac, renal, or hepatic dysfunction. Drug metabolism in the aging adult is significantly decreased due to natural deficiencies in organ function. Some studies suggest glomerular filtration rate is lowered by almost 66 % when reaching the age of 80 years old [36]. Decreased hepatic enzymes, lower blood flow to the liver, and decreased liver mass all exacerbate an elderly patient's response to additional medication—especially in the setting of polypharmacy. Any signs of decreased cardiac output stemming from valvular or cardiomyopathies will further impact renal and hepatic clearance [37]. To this end, the American Geriatric Society recommends not only beginning treatment with low doses but also titrating slowly as well—requiring the clinician to meet with the patient on a more frequent basis [38]. Adopting this protocol most likely will lead to prolonged treatment duration and, consequently, patient compliance issues. Articulating clear treatment goals will remain a high priority for the physician. Since pain is generally underreported in the elderly patient, careful attention must be paid to any and all complaints, usually mandating the use of more extensive pain assessment techniques [38, 39].

Current guidelines suggest beginning treatment with either alpha-2 delta ligands, tricyclic antidepressants, tramadol, or opioids. Of these four, TCAs and alpha-2 delta ligands are the most popular initial interventions [35••]. The mechanism behind the efficacy of TCAs is thought to be the result of decreasing sensory perception between the brainstem and the spinal cord [40]. TCAs inhibit the reuptake of serotonin and norepinephrine—the major neurotransmitters involved in this inhibitory pathway. Two classes of TCAs exist: secondary amines and tertiary amines. Several clinical trials have assessed the differences in effectiveness between these two groups and concluded tertiary amines showed greater efficacy in reducing pain than secondary amines or placebo. However, treatment with tertiary amines such as clomipramine or amitriptyline does not come without a cost. These options tend to increase postural hypotension and sedation [35••, 40].

The alpha-2 delta ligands, gabapentin and pregabalin, are popular amongst clinicians for treating PHN and other types of neuropathic pain [35••]. Gabapentin can be administered as an immediate release or extended-release formulation [41]. A Cochrane review demonstrated both were more effective in treating PHN than placebo. Two forms of extended-release gabapentin are particularly interesting, gastroretentive gabapentin, and gabapentin enacarbil. The gastroretentive preparation slowly releases the drug for up to 15 h after taken with food as compared with 2 h for gabapentin [35••, 41]. Separate studies have aimed to determine the efficacy of this treatment option, with each yielding differing conclusions. In one, a statistically significant reduction in pain scores resulted after 10 weeks, while second and third studies demonstrated no improvement over a 10-week treatment period (albeit the latter two used the strict imputation method known as "baseline observation carried forward") [35••, 41]. Regardless, gastroretentive gabapentin falls in line with the European Federation of the Neurological Society guidelines and can be recommended as first-line treatment. Patients should begin a starting dose of 300 mg once daily and titrate upwards to 1800 mg/day over the course of several weeks [35••, 41]. The most common side effects are dizziness and somnolence, and those with renal impairment should have adjustments in their dose. Because gabapentin is excreted without being metabolized, those with hepatic impairment are not exposed to additional harm.

Gabapentin enacarbil, previously known as XP13512, is an extended release prodrug of gabapentin with higher absorption potential [35••, 42]. Traditional gabapentin saturates transporters only in a limited part of the small intestine, while enacarbil has the ability to employ high-capacity nutrient transporters along the entirety of the small intestine. The chemical modification inherent of this novel drug allows for patients to have a more dependable treatment experience along with decreased frequency of administration. In one clinical trial, enacarbil was shown to have the same efficacy at 2400 and 3600 mg/day versus 1200 mg/day. The recommended starting dose is 600 mg for the first 3 days, and then

1200 mg per day thereafter. Despite the evidence of symptomatic control with enacarbil's use versus placebo, the deficiency of data comparing the drug to other formulations limits the amount of confidence one can have when recommending this as a treatment option [35••, 42].

Pregabalin is another treatment modality for PHN that has a mechanism closely related to gabapentin [43]. The recommended starting dose is 150 mg/day split in two or three doses. Several trials have shown patients experience maximum benefit when titrated to 600 mg/day (if symptoms do not improve after 2 to 4 weeks). The oral bioavailability of pregabalin is quite high at over 90 % when taken at 900 mg/day but decreases to 27 % when doses exceed 4800 mg/day [35••, 43]. Virtually none of the drug is metabolized by the liver and is therefore excreted by the kidneys unchanged. For this reason, dose adjustments must be considered when dealing with the typically older PHN patient. In one 8-week clinical trial, some patients reported an improvement in pain scores after just 1 day and had statistically significant reduction throughout the remainder of the study. The attractiveness in pregabalin rests with its lack of pharmacokinetic drug interactions—similar to gabapentin—and its linear dose to plasma concentration relationship. This predictable response allows for the patient to feel more in control since there is an expectation of what will happen when a dose is modified. As with other PHN pharmaceuticals, adverse effects ranged from dizziness, somnolence, and edema to ataxia and headache [43, 44].

Opioids are reserved for adjunct treatment, with both strong and weak formulations being utilized [20]. A randomized, controlled trial suggested—with borderline significance—a greater reduction in pain and lower number needed to treat with opioids compared to TCAs. Interestingly, despite the weak correlation, patients who participated in the study preferred opiates to TCAs for reducing their pain despite side effects such as constipation, nausea, dizziness, or drowsiness. Additionally, this study demonstrated that long-term use of opioids carried no increased risk of cognitive impairment even in the face of overwhelming scientific literature suggesting the opposite [20]. Elderly patients may also experience increased risk of falling and hip fractures when under the influence of opioid medications. When considering all of the evidence, the consensus from the scientific community points to a weak recommendation for opioid treatment—partly due to the lack of long-term studies of chronic opioid use [20, 35••].

Conclusion

Although various treatment algorithms exist for managing PHN, there are clearly defined guidelines in place that dictate first-line therapy. It is universally accepted to begin treatment with a tricyclic antidepressant (such as amitriptyline, nortriptyline, and desipramine) or a gabapentinoid (gabapentin and pregabalin) [35••]. Choosing one formulation over another within a drug-class (short-acting vs long-acting gabapentin) depends on the patient's overall clinical picture. Both TCAs and gabapentinoids have side effect profiles that may interfere with long-term treatment goals. For this reason, providers may wish to use topical lidocaine or tramadol (usually second- or third-line therapy) first. Considering TCAs, gabapentinoids and opioids have separate mechanisms, their concurrent use is safe for patients who do not respond to one drug alone. Combination therapy with systemic and topical agents is currently the most popular regimen. Factors beyond the clinician's control, such as reimbursement policies, also plays a role when deciding the appropriate medication for the treatment of PHN [35••]. The frequency of administration, efficacy, and tolerability of agents will remain the most important factors when navigating treatment routes—especially when dealing with an older patient demographic [35••].

Compliance with Ethical Standards

Conflict of Interest Graham R. Hadley, Julie A. Gayle, Juan Ripoll, Mark R. Jones, Rachel J. Kaye, and Alan D. Kaye declare that they have no conflict of interest.

Charles E. Argoff declares personal fees for consultant work for Pfizer, Depomed, and XenoPort and honoraria from Depomed and XenoPort.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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