

# Unmet Need in the Treatment of Postherpetic Neuralgia

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## Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is a chronic pain syndrome that can develop following an episode of herpes zoster. Also known as shingles, herpes zoster results from reactivation of varicella zoster virus (VZV) contracted years earlier (usually as chicken pox). Herpes zoster affects approximately 1 million people in the United States each year and the lifetime risk of developing the disease is about 30%.<sup>1</sup> Prior to the appearance of a rash, there is often pain, itching, or tingling in the area where the rash will develop. This prodromal period may last anywhere from 1 to 5 days before the rash appears. The hallmark of herpes zoster is a painful, blistering rash that is localized to 1 or 2 dermatomes on 1 side of the body; a dermatome is an area of skin served by a single spinal nerve. The blisters usually scab over in 7 to 10 days and the lesions clear within 2 to 4 weeks.

PHN is a condition in which neuropathic pain persists beyond the clearing of the rash.<sup>2</sup> As many as 20% of patients with herpes zoster develop PHN and the risk increases with age.<sup>3</sup> The duration of pain required for a diagnosis of PHN varies from 1 to 6 months after onset of the rash<sup>4</sup>; for some patients, pain can persist longer (years). The rate of spontaneous remission decreases markedly after 6 months.<sup>5</sup>

The risk of PHN after herpes zoster increases with age, and the elderly are the most frequently and seriously affected.<sup>1,6,7</sup> A retrospective population-based study reported that the percentage of patients with herpes zoster who developed PHN (defined as at least 90 days of documented pain) increased from 5% in patients younger than 60 years to 10% in patients aged 60 to 69 years, to 17% in those aged 70 to 79 years, and to 20% in those 80 years or older.<sup>8</sup> Aside from age and the age-related decline in cell-mediated immunity, additional risk factors for PHN include female gender, greater rash severity, greater acute pain, the presence of a prodrome, and being immunocompromised.<sup>3,9,10</sup> A multivariate logistic regression analysis identified advanced age and deep pain at the initial visit to the pain clinic as significant predictors for PHN.<sup>11</sup> Elderly people represent the fastest growing segment of the population in western countries.<sup>12</sup> In the 2010 US Census, 40.3 million people, or 13% of the total population, were 65 years or older, more than 13 million were 75 years or older, and more than 5 million were 85 years or older.<sup>13</sup> Thus, the incidence of PHN is expected to increase as the population ages.

## Abstract

The efficacy of first-line therapeutic agents for postherpetic neuralgia (PHN) has been established in randomized, controlled clinical trials. However, pain in PHN is often refractory to treatment. Many of the patients with PHN are elderly, with additional issues of polypharmacy and comorbidity. They experience various types of pain, suggesting that more than 1 pathophysiologic pain mechanism is involved. PHN adversely affects health-related quality of life. Up to this point, no single best treatment has been identified for PHN. Pharmacological treatments for PHN are inadequate, and many patients are undertreated. Suboptimal treatment can be related to intolerable side effects of medications, long titration periods to reach the effective dosage, inadequate dosing, poor compliance with dosing schedules, and low treatment satisfaction. Inadequate therapeutic response leads more than half the patients with PHN treated with either gabapentin or pregabalin to switch to another class of medication, and more than 30% of patients to add on another class of medication. Safety and tolerability are important considerations in therapy, especially in the elderly. Few patients with PHN and physicians are satisfied with the currently available treatments. Thus, the effective management of postherpetic neuralgia remains an ongoing challenge. New and improved treatment options are therefore needed for the effective management of PHN.

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For author information and disclosures, see end of text.

The severity of pain in PHN ranges from mild to excruciating.<sup>14</sup> Patients with PHN have described their pain as a constant, deep aching or burning, as a paroxysmal, lancinating pain, and one that may be provoked by stimuli that are normally not painful (allodynia).<sup>15</sup> The pain can persist for months and sometimes years after resolution of the initial herpes zoster rash.<sup>16,17</sup> Health-related quality of life is adversely affected in patients with PHN and the pain may negatively affect patients' lives across 4 health domains: physical, psychological, functional, and social.<sup>18</sup>

The pathophysiology of PHN is incompletely understood. After reactivation of the VZV, the virus replicates and spreads along a spinal or cranial nerve toward the skin, potentially causing nerve damage. In addition, reactivation of the VZV in herpes zoster may spread viral particles into the dorsal horn of the spinal cord through peripheral sensory nerves. Thus, pain may involve both the peripheral and central nervous systems. This reactivation is also accompanied by hemorrhage, immune response, and destruction of peripheral and central neurons and their fibers.<sup>19</sup> As damaged peripheral nerves develop lowered activation threshold for pain, sensory receptors become further sensitized, producing hyperexcitability and spontaneous discharge.<sup>3,19,20</sup> In response to increased peripheral nerve activity, dorsal horn neurons in the spinal cord may become altered, impairing descending inhibition of pain, and leading to central sensitization.<sup>19,20</sup> With the loss of peripheral sensory fibers, central processes of surviving axons may develop aberrant connections, and the resulting anatomical and functional reorganization may lead to the allodynia and spontaneous pain frequently observed in PHN.<sup>19,21-24</sup>

### Strategies to Prevent PHN

Strategies directed at the prevention of PHN include antiviral drugs and vaccination. Antiviral drugs (eg, acyclovir, famciclovir, and valacyclovir), when administered within 72 hours of rash onset in herpes zoster, can limit viral replication, reduce rash duration, and reduce the risk and/or duration of PHN.<sup>25</sup> However, antiviral drugs do not completely prevent PHN.<sup>9,26</sup> The vaccination strategy seeks to boost VZV-specific immunity of VZV-seropositive adults, and prevent the latent infection in sensory ganglia from reactivating. Results of the Shingles Prevention Study showed statistically significant reductions in the burden of illness due to herpes zoster (61%), incidence of herpes zoster (51%), and incidence of PHN (67%).<sup>5</sup> The vaccine is indicated for the prevention of herpes zoster in individuals 50 years or older.<sup>27</sup> However, the vaccine alone will likely not lead to eradication of PHN. As of 2008, only 6.7% of adults 60 years or older

reported having received the herpes zoster vaccination.<sup>28</sup> In 2009, an estimated 10% of adults 60 years or older reported having received the vaccination.<sup>29</sup> Furthermore, Gilden et al reported that even if every healthy adult 60 years or older were vaccinated, there would still be approximately 500,000 cases of herpes zoster annually, with 200,000 experiencing PHN.<sup>17</sup>

### Limitations of PHN Treatment Options

The type and duration of pain in PHN can be highly variable, suggesting that multiple pathophysiological mechanisms may be involved. Pain mechanisms may also differ from one patient to another. These factors, in addition to the incomplete understanding of the causes of pain associated with PHN, make PHN more difficult to treat.

Numerous medications have been evaluated in clinical trials and are associated with a reduction in PHN-related pain (**Table**).<sup>30-37</sup> Gabapentin, pregabalin, topical lidocaine, topical capsaicin, and gabapentin enacarbil have received FDA approval specifically for the PHN indication. However, the American Academy of Neurology, the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain, and the European Federation of Neurological Societies Task Force Guidelines also recommend tricyclic antidepressants (amitriptyline, nortriptyline, or desipramine) and opioids as first-line treatments for PHN.<sup>30-32</sup> Pain in PHN is often refractory to treatment,<sup>2,7,19</sup> and many patients require more than 1 agent to achieve significant pain relief.<sup>6,38-42</sup> In addition, approximately 40% to 50% of patients with PHN do not respond to any treatment,<sup>43</sup> and other patients experience limited efficacy.

Limited efficacy may be due to the inherent properties of the therapies, but treatment of PHN is often accompanied by intolerable side effects,<sup>18,44</sup> which may prevent attainment of therapeutic dosages of oral PHN therapies. This in turn causes inadequate treatment of pain such that patients need to switch medications or add onto existing medications (**Figure 1**). Neither one of these options guarantees efficacy (dashed lines in Figure 1), and there may still be side effects and/or poor tolerability. The adding on of medications further complicates polypharmacy, a common condition in the elderly.

The tricyclic antidepressants have adverse effects in addition to potential drug-drug interactions,<sup>45</sup> and consequently have been identified by the American Geriatrics Society as a class of drugs to avoid in elderly patients.<sup>46</sup> Anticonvulsant medications for PHN have been associated with high incidences of dizziness and somnolence.<sup>47,48</sup> Opioids have numerous adverse effects including constipation, nausea, dizziness/

■ **Table.** Therapies for Postherpetic Neuralgia

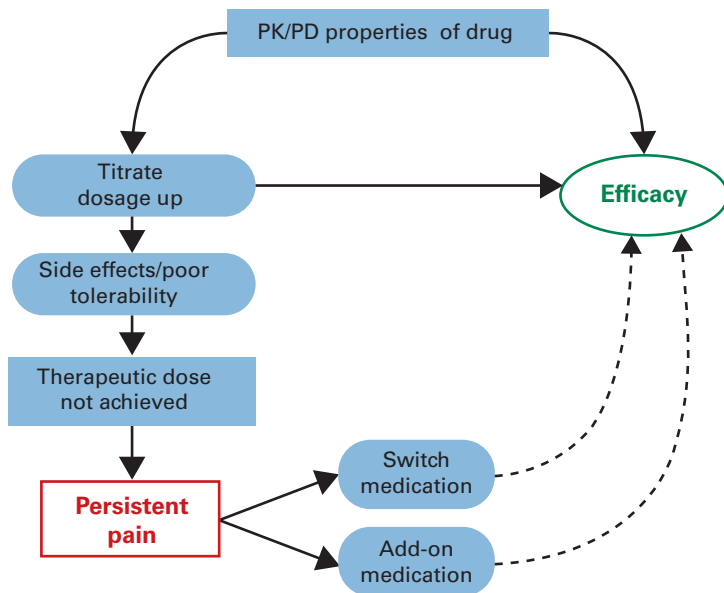
Medication	Dosage (Initial and Titrating)
<b>Tricyclic Antidepressants (TCAs)</b>	
Nortriptyline <sup>30,31,a,b</sup>	10-25 mg at bedtime; increase by 25 mg/day weekly if tolerated; usual maintenance dosage 75 mg/day; maximum dosage 125 mg/day.
Desipramine <sup>30,31,a,b</sup>	10-25 mg/day; increase every 3 days as necessary; usual effective dosage 50-150 mg/day; maximum dosage 150 mg/day.
<b>Anticonvulsants/Calcium Channel <math>\alpha_2</math>-<math>\delta</math> Ligands</b>	
Gabapentin <sup>32</sup>	Day 1: 300 mg, Day 2: 600 mg (divided BID), Day 3: 900 mg (divided TID). Dosage titrated up as needed to daily dosage of 1800 mg. Efficacy range in clinical studies: 1800 mg/day to 3600 mg/day. Additional benefit of dosages >1800 mg/day not demonstrated.
Pregabalin <sup>33</sup>	Begin at 150 mg/day in divided dosages (75 mg BID or 50 mg TID); may increase to 300 mg/day within 1 week; maximum dosage 600 mg/day.
Gabapentin enacarbil <sup>34</sup>	Begin at 600 mg in AM for 3 days, then increase to 600 mg BID on day 4.
<b>Opioids</b>	
Oxycodone (dosage given for morphine equivalents) <sup>30</sup>	2.5-15 mg every 4 hours as needed. After 1-2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting agent as needed.
Tramadol <sup>30,35</sup>	For patients requiring rapid onset of analgesic effect: 50-100 mg every 4-6 hours as needed, not to exceed 400 mg/day. For patients not requiring rapid onset of analgesic effect: 25 mg/day in AM and titrated in 25-mg increments as separate doses every 3 days to reach 100 mg/day (25 mg QID). After titration: 50-100 mg every 4-6 hours as needed, not to exceed 400 mg/day. Adjustment of daily dosage recommended for patients older than 75 years.
<b>Topical Medications</b>	
Lidocaine 5% patch <sup>36</sup>	Apply up to 3 patches to intact skin once for up to 12 hours or within a 24-hour period. Each patch contains 700 mg of lidocaine.
Capsaicin 8% patch <sup>37</sup>	Apply up to 4 patches to dry, intact skin in a single, 60-minute application. Each patch contains a total of 179 mg capsaicin. <i>Note:</i> a topical anesthetic is applied prior to capsaicin patch application.
<p><sup>a</sup>Off-label use.  <sup>b</sup>Use with caution in elderly.            BID indicates twice daily; CNS, central nervous system; TID, 3 times daily; QID, 4 times daily.</p>	

vertigo, somnolence, vomiting, pruritus, and CNS stimulation; the elderly are more sensitive to opioid CNS side effects. The long-term administration of opioids is also controversial because of concerns over development of tolerance (ie, higher dosages are required for similar pain relief) and the potential for abuse and dependency. Furthermore, drugs commonly used in the elderly, such as antiarrhythmics, beta-blockers, calcium channel blockers, hormonal therapies, selective serotonin/norepinephrine reuptake inhibitors, statins, and warfarin, can contribute to clinically relevant drug-drug interactions when administered with most opioids.<sup>49</sup> Drug-drug interactions may include pharmacokinetic interactions, which affect the way

the body absorbs, distributes, metabolizes, or eliminates the drug, or pharmacodynamic interactions which occur when another drug alters the clinical effect of the first drug.

Topical therapies, such as the lidocaine patch or the capsaicin patch, can reduce pain in PHN without significant systemic effects, a characteristic that may be beneficial in the elderly population. Their localized action may also be of use for PHN affecting the face or extremities. However, these treatment options tend to be more short acting. Moreover, for patients whose pain is more widespread, topical treatments are limited by the inherent localized nature of their application. Many patients report only partial relief with the

■ **Figure 1.** Algorithm for the Treatment of Postherpetic Neuralgia

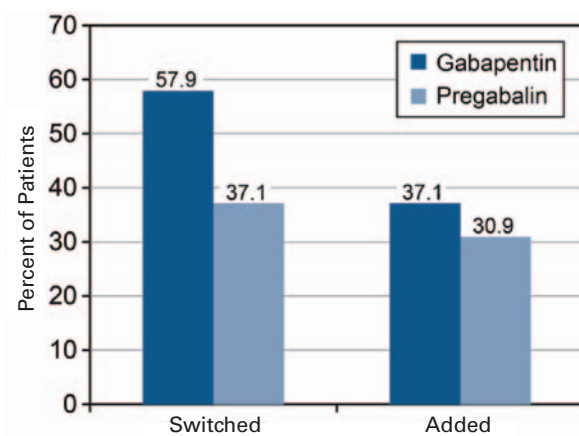


PD indicates pharmacodynamic; PK, pharmacokinetic. Dashed lines indicate that switched-to or added-on medication does not necessarily provide efficacious pain relief and may also be associated with side effects/poor tolerability.

lidocaine patch, and some patients discontinue therapy due to local skin irritation.<sup>50</sup> Patients may require 2 weeks of therapy to determine if the patch provides meaningful benefit.<sup>50</sup>

Special care is required for the application of the capsaicin patch, which needs to be administered by a physician or under the close supervision of a physician, with specific instructions to use nitrile gloves (and not latex gloves) when handling the capsaicin patch.<sup>36</sup> Prior to patch application,

■ **Figure 2.** Percentage of Patients Taking Gabapentin or Pregabalin for Postherpetic Neuralgia Who Switched From That Therapy or Added a Therapy<sup>53</sup>



the affected area is treated with a topical anesthetic to reduce application site pain. Once the patch is removed, the skin site is cleansed with a cleansing gel, and all cleansing materials are disposed of in accordance with local biomedical waste procedures.<sup>36</sup>

**Inadequate Therapy**

Patients often report intolerable treatment-related side effects. Some of the effects of pain medications can be addressed by titrating the drug dosages.<sup>18</sup> A 10-day titration to a daily dosage of 200 mg (50 mg 4 times daily) with immediate-release tramadol was initiated at 50 mg/day and gradually increased by 50 mg increments every 3 to 4 days.<sup>34</sup> A slower rate of initiating tramadol therapy improved tolerability, with fewer patients discontinuing due to dizziness or vertigo.<sup>51</sup> Similarly, to avoid the adverse effects of confusion, somnolence, and fatigue, the dosage of gabapentin is titrated up slowly. However, drug titration may require several weeks to reach the effective dosage. Starting at 100 to 300 mg/day and increasing by 100 to 300 mg/day until the

target dosage is reached means that a full therapeutic effect is not reached for 8 weeks or longer,<sup>52</sup> leaving patients with PHN suffering for a significant period of time before their pain is adequately treated.

In a retrospective administrative claims database analysis (n = 1645 patients with PHN), a low percentage of patients treated with gabapentin (14%) reached the target dosage (1800 mg/day: 600 mg 3 times daily), and it took patients 10 weeks to reach 1800 mg/day dosage of gabapentin, and 9.2 weeks to reach a dosage of pregabalin of 300 mg/day or greater (a dosage with similar efficacy to 1800 mg/day gabapentin).<sup>53</sup>

Another reason for suboptimal treatment in patients with PHN involves patterns of medication use. Many patients report taking dosages of their prescribed medications that were less than the amount recommended in the prescribing information. Patients 65 years and older who responded to a newspaper survey reported a mean daily amitriptyline dosage of 37 mg (effective dosage 50 mg/day or higher) and a mean gabapentin dosage of 620 mg (package labeling recommends between 900 mg/day and 1800 mg/day).<sup>44</sup> In the retrospective claims database analysis of gabapentin and pregabalin use, the mean daily dosages were 826 mg for gabapentin and 187 mg for pregabalin<sup>53</sup>; both were below the recommended daily dosages of 1800 mg/day for gabapentin and 300 mg per day for pregabalin. Suboptimal dosing may produce inadequate

treatment response, causing the patient to switch therapy, add on medications, or discontinue therapy. From the retrospective claims database study with gabapentin and pregabalin in PHN, more than half the patients switched during treatment to another class of medications, and one-third added a class of medications (Figure 2).<sup>53</sup> Opioids were added by over 50% of the patients on gabapentin and pregabalin (Figure 3A).<sup>53</sup> Among the patients who switched their therapy, approximately one-third switched to opioids (Figure 3B).<sup>53</sup>

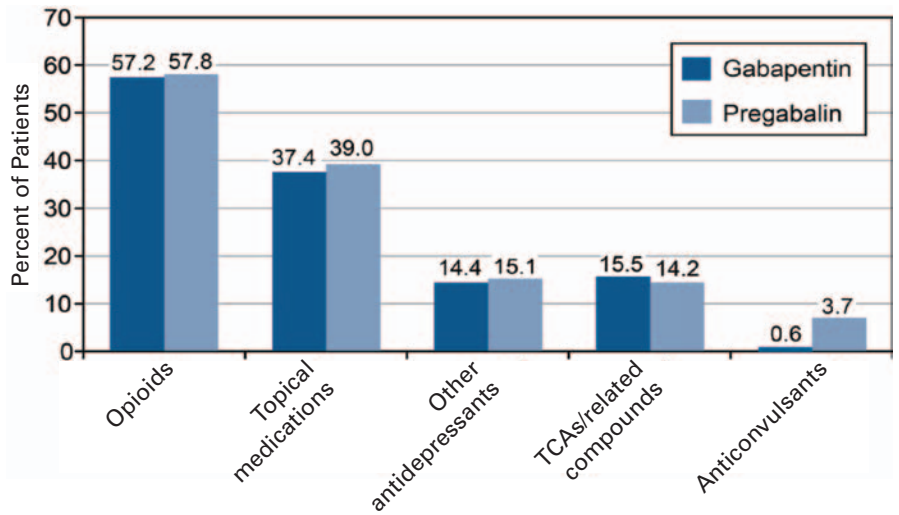
Compliance with the dosage and dosing regimen also contribute to suboptimal treatment. The dosing frequencies for the oral therapeutic agents listed in Table 1 range from once daily to 6 times daily. Pharmacokinetic parameters dictate the dosing regimen of drugs. For example, the recommended maintenance dosage of immediate-release gabapentin for PHN is 1800 mg/day, administered in 3 divided doses.<sup>31</sup> This dosing regimen is consistent with gabapentin's elimination half-life of 5 to 7 hours following oral administration.<sup>54,55</sup> However, more frequent dosing is often associated with poor compliance. A systematic review of studies demonstrated an association between dosage regimens and medication compliance. Mean dose-taking compliance declined as the number of daily doses increased: 1 dose, 79%; 2 doses, 69%; 3 doses, 65%; and 4 doses, 51%.<sup>56</sup>

**Unmet Need**

The increased prevalence of PHN in the aging population is associated with increased healthcare utilization and costs as well as patient disability.<sup>2,57</sup> Patients with PHN have an aver-

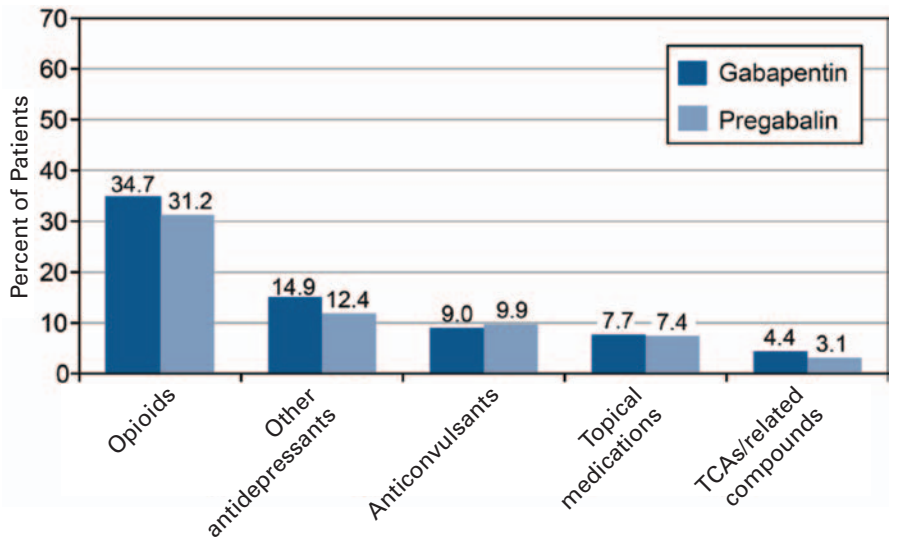
age of 5 outpatient visits compared with 2 outpatient visits for herpes zoster patients without PHN, and have a mean of 17.1 prescriptions filled compared with a mean of 5.5 prescriptions for herpes zoster patients without PHN.<sup>58</sup> Available treatment options for PHN are limited, and often require several weeks to reach target dosing, during which time patients have inadequate pain control. For many elderly patients with PHN, pain is severe and debilitating, and dissatisfaction with treatment

■ **Figure 3A.** Classes of Medications Added Among Patients Treated With Gabapentin or Pregabalin<sup>53</sup>



TCA indicates tricyclic antidepressant. Percentages are of patients who added or switched and categories are not mutually exclusive.

■ **Figure 3B.** Classes of Medications to Which Patients Treated With Gabapentin or Pregabalin Switched<sup>53</sup>



TCA indicates tricyclic antidepressant. Percentages are of patients who added or switched and categories are not mutually exclusive.

is high.<sup>44</sup> A recent national study on practice patterns found that few patients with PHN and physicians were satisfied with the treatments currently available.<sup>59</sup> Effective strategies for the treatment of pain associated with PHN remains an unmet public health need.<sup>60</sup> With the increasing numbers of elderly persons in the population and the current inadequate outcomes of PHN treatment, new treatment options for PHN are needed.

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**Authorship information:** Concept and design; critical revision of the manuscript for important intellectual content; administrative, technical, or logistic support; and supervision.

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