

# Treating herpes zoster and postherpetic neuralgia: An evidence-based approach

When are corticosteroids appropriate for patients with herpes zoster? Which tricyclics are best for frail and elderly patients with PHN pain? And when should you consider opioids? Read on.

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**P**ostherpetic neuralgia (PHN) is a management challenge—because of its severity, long duration, and potential for debilitation, often in the highly vulnerable elderly population. And, as the most common complication of an acute episode of herpes zoster (shingles) in an immunocompetent person, PHN is likely no stranger to your practice.

Herpes zoster is one of the most common neurological problems, with an incidence of up to 1 million new cases per year in the United States.<sup>1</sup> Although the precise number for the prevalence of PHN in the United States is unknown, investigators estimate it at 500,000 to 1 million.<sup>2</sup>

Major risk factors for development of PHN after an episode of herpes zoster include:

- older age

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Gabapentin or pregabalin, followed by a tricyclic antidepressant, can be added if conventional analgesics are not effective for herpes zoster pain.

- greater acute pain during herpes zoster
- greater severity of rash.<sup>3,4</sup>

PHN is commonly defined as “dermatomal pain that persists 120 days or more after the onset of rash.”<sup>5</sup> The pain of PHN has been characterized as a stimulus-dependent continuous burning, throbbing, or episodic sharp electric shock-like sensation<sup>6</sup> and as a stimulus-dependent tactile allodynia (ie, pain after normally nonpainful stimulus) and hyperalgesia (exaggerated response to a painful stimulus). In addition, some patients experience myofascial pain secondary to excessive muscle guarding. Chronic pruritus can be present.

More than 90% of patients who have PHN have allodynia,<sup>7</sup> which tends to occur in areas where sensation is relatively preserved. Patients also feel spontaneous pain in areas where sensation is lost or impaired.

In this article, we review the evidence for the range of treatments for acute herpes zoster and PHN, as well offer preventive strategies for herpes zoster.

### Acute herpes zoster: Start antivirals early

Evidence-based treatment of acute herpes zoster includes antiviral drugs and analgesics.

**Antiviral agents** suppress viral replication and have a beneficial effect on acute and chronic pain. Acyclovir (800 mg, 5 times a day), valacyclovir (1000 mg, every 8 hours), and famciclovir (500 mg, every 8 hours) are antivirals commonly used to treat herpes zoster. All 3 drugs have comparable efficacy and safety profiles.

In a meta-analysis of patients older than 50 years who were treated with acyclovir or placebo, pain persisted in 15% of the acyclovir-treated group, compared with 35% of the placebo group.<sup>8</sup> In terms of duration, a study comparing famciclovir treatment with placebo showed that subjects in the placebo group had persistent pain for 163 days, whereas famciclovir-treated patients had pain for 63 days.<sup>9</sup>

Based on this evidence, antiviral medications are strongly recommended for treating herpes zoster, especially for patients at increased risk of developing PHN. Antiviral treatment should be started within 72 hours of the onset of the rash.

No good evidence supports the efficacy of antiviral treatment administered 72 hours after the onset of rash. One uncontrolled trial, however, examined the effectiveness of acyclovir started before vs after 72 hours; the difference in pain persistence was not significant between

the groups, suggesting acyclovir has benefit even when given after 72 hours.<sup>10</sup>

In clinical practice, the diagnosis of herpes zoster is often not made within 72 hours of symptom onset; nevertheless, it is important to identify patients who could still benefit from antiviral medication even when treatment is started relatively late in the disease course. This is especially true in ocular zoster, because viral shedding may continue beyond 72 hours.<sup>11</sup>

**Analgesics** are part of a practical approach for managing herpes zoster–associated pain that begins with a short-acting opioid in combination with acetaminophen or a nonsteroidal anti-inflammatory (NSAID) agent. Gabapentin or pregabalin, followed by a tricyclic antidepressant, can be added if conventional analgesics are not entirely effective. The analgesic regimen should be tailored to the patient’s needs and tolerance of adverse effects. If pain control is inadequate or adverse effects are intolerable, consider referring the patient to a pain management center for possible interventional modalities.

**Corticosteroids** are not recommended routinely for treatment of herpes zoster; you can try them in otherwise healthy older adults, however, if antiviral therapy and analgesics do not relieve pain. In 2 double-blind controlled trials, a combination of acyclovir and corticosteroids for 21 days did not decrease the incidence of PHN—although some benefit was seen in terms of patients’ return to normal activities, cessation of analgesic therapy, and improved sleep.<sup>12,13</sup>

### Evidence-based treatment options for PHN

Pharmacotherapy for PHN includes anticonvulsants, tricyclic antidepressants, opioids, and topical agents. Invasive interventions have a limited but important role in the management of PHN pain in clinical practice.

**Calcium channel-blocking anticonvulsants** gabapentin and pregabalin are safe and relatively well tolerated. They can be used as first-line agents for PHN, starting with a low dosage and titrating up, based on effectiveness and tolerability.

**Gabapentin** is FDA approved for the treatment of PHN. The starting dosage is 100 to 300 mg taken at night, titrated as needed by 100 to 300 mg every 3 to 5 days, to as high a dosage as 1800 to 3600 mg/d in 3 or 4 divided doses. In 2 large, randomized controlled trials,

gabapentin produced a statistically significant reduction in pain ratings and improved sleep and quality of life.<sup>14,15</sup> Adverse effects include somnolence, dizziness, peripheral edema, visual adverse effects, and gait and balance problems.

Because gabapentin is excreted by the kidneys, take care when using it in patients with renal insufficiency. Gabapentin clearance is linearly related to creatinine clearance and is decreased in the elderly and in individuals with impaired renal function. Hence, the gabapentin dose and the frequency of dosing must be adjusted in these patients.

In patients on hemodialysis, plasma gabapentin levels can be maintained by giving a dose of 200 to 300 mg 4 hours after hemodialysis.<sup>16</sup>

**Extended-release gabapentin.** The FDA recently approved an extended-release gabapentin formulation for PHN. Approval was based on a 12-week pivotal study and 2 adjunct studies. In a multicenter, randomized, double-blind, parallel-group, placebo-controlled, 12-week study evaluating the efficacy, safety, and dose response of 3 doses, extended-release gabapentin was effective at 1200 mg/d dosing. The initial recommended dose is 600 mg, once daily for 3 days, followed by 600 mg, twice daily, beginning on Day 4.<sup>17</sup> The premise is that the extended-release preparation improves bioavailability of the active drug and, therefore, reduces the incidence of adverse effects, compared with regular gabapentin.

Overall, evidence is mixed. Two randomized controlled trials of extended-release gabapentin showed benefit (ie, reduced pain score on a numerical rating scale) with twice-a-day dosing (600 mg in the morning and 1200 mg at night), compared with a once-daily 1800-mg dose as well as placebo, for reduction in intensity of pain<sup>18</sup> and specific pain quality.<sup>19</sup> In another trial, however, extended-release gabapentin, 1800 mg once daily, did not show any benefit compared with placebo.<sup>20</sup>

**Pregabalin** is also FDA approved for PHN. The effective dosage range is 150 to 600 mg/d. Pregabalin provided significantly superior pain relief and improved sleep scores compared with placebo in 776 patients with PHN.<sup>21</sup> Adverse effects include weight gain, dizziness, and somnolence. Titrate the dosage slowly in the elderly.

**Sodium channel-blocking anticonvulsants** topiramate, lamotrigine, carbamazepine, oxcarbazepine, levetiracetam, and valproic acid are *not* FDA approved for PHN. These agents may be a treatment option, however, for patients with PHN who do not respond to con-

ventional therapy. In an 8-week randomized controlled trial, patients treated with divalproex sodium (valproic acid and sodium valproate), 1000 mg/d, experienced significant pain relief compared with placebo-treated patients.<sup>22</sup> Adverse effects included vertigo, hair loss, headache, nausea, and diarrhea.

**Tricyclic antidepressants**, including amitriptyline, desipramine, and nortriptyline, might work by (1) inhibiting norepinephrine and serotonin uptake, (2) sodium-channel blockade, or (3) another mechanism that is unclear. Although amitriptyline is the most studied tricyclic antidepressant for PHN, available evidence and clinical experience suggest that nortriptyline and desipramine have comparable efficacy and are better tolerated.<sup>23,24</sup>

Nortriptyline and desipramine are preferred in frail and elderly patients. Start therapy with 10 to 25 mg nightly, titrating as tolerated every 2 weeks to 75 to 150 mg as a single daily dose. Adverse effects include dry mouth, fatigue, dizziness, sedation, urinary retention, orthostatic hypotension, weight gain, blurred vision, QT interval prolongation, constipation, and sexual dysfunction.

**Serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants.** Use of such agents as duloxetine and venlafaxine in PHN patients is extrapolated from their proven efficacy in treating diabetic neuropathy and other neuropathic pain conditions. Try duloxetine if your patient does not respond to or tolerate a tricyclic. The recommended dosage is 60 to 120 mg/d in 2 divided doses.<sup>25</sup>

Two randomized, 12-week, double-blind, placebo-controlled trials using duloxetine 60 mg once a day and 60 mg twice a day for diabetic peripheral neuropathy concluded that 120 mg was safe and effective in treating diabetic peripheral neuropathy, but 120 mg was not as well tolerated as 60 mg once a day.<sup>25</sup>

Monitor liver function periodically in patients taking duloxetine. Alternatively, you can give venlafaxine; the recommended dosage is 75 to 225 mg/d.<sup>26</sup>

**Opioid analgesics** are recommended as second- and third-line agents for PHN. Adverse effects include nausea, pruritus, sedation, confusion, constipation, hypogonadism, and risk of developing tolerance and abuse.

A double-blind crossover trial evaluated the analgesic efficacy of oral oxycodone; treatment resulted in significant reduction of allodynia, steady pain, and spontaneous paroxysmal pain. Oxycodone treatment resulted in superior scores

Available evidence and clinical experience suggest that nortriptyline and desipramine have comparable efficacy and are better tolerated than amitriptyline for PHN.

Acupuncture and transcutaneous electrical nerve stimulation do not appear to be effective for PHN relief.

of global effectiveness, disability reduction, and patient preference, compared with placebo.<sup>27</sup>

In a randomized crossover trial, the combination of gabapentin and morphine was superior to either of these medications alone in relieving pain in PHN.<sup>28</sup>

**Tramadol**, an atypical opioid, has a weak  $\mu$ -opioid receptor agonist effect and inhibits reuptake of serotonin and norepinephrine. Avoid using it in patients with a history of seizures. The maximum recommended dosage is 400 mg/d. An extended-release formulation of tramadol is also available.

Tramadol provided superior pain relief and improved quality of life in PHN patients in a randomized placebo-controlled trial.<sup>29</sup>

**Tapentadol** has weak  $\mu$ -opioid receptor agonist activity; norepinephrine reuptake inhibition is more predominant than serotonin reuptake inhibition. This drug is also available as an extended-release formulation. The maximum recommended dosage is 600 mg/d.

Avoid using tapentadol in patients with a history of seizures. *Note:* Although there is no scientific evidence regarding the use of tapentadol in neuropathic pain, we use it often in our practice.

### Topical therapies

Treating PHN with a topical agent is associated with relatively fewer adverse effects than what has been seen with oral therapy because systemic absorption is minimal.

**Lidocaine** is available as a transdermal patch and as a topical gel ointment. The 5% lidocaine patch is FDA approved for treating PHN. Lidocaine, a sodium-channel blocker, is useful for treating patients with clinical evidence of allodynia. You can cut a patch to fit the affected area; a maximum of 3 patches can be used simultaneously for 12 hours on, 12 hours off. If helpful, the patch can be left in place for 18 hours.<sup>30</sup>

In 2 open-labeled, nonrandomized prospective studies, patients treated with the lidocaine patch had reduced intensity of pain and improved quality of life.<sup>31,32</sup>

If lidocaine patches are not available, or affordable, or if a patient has difficulty applying them, use 5% lidocaine gel instead.

**Capsaicin** topical cream is sold in 2 concentrations: 0.025% and 0.075%. An extract of hot chili peppers, capsaicin acts as an agonist at the vanilloid receptors. The recommended dosage is 3 or 4 times a day. Initial application

causes burning to become worse, but repeated use results in diminished pain and hyperalgesia.

A 6-week, blinded parallel study, followed by a 2-year open label follow-up, showed that the 0.075% dose of topical capsaicin cream relieved pain in 64% of patients; pain was relieved in 25% of placebo-treated patients.<sup>33</sup>

An 8% capsaicin patch is FDA approved for treating PHN. The patch must be applied by a health care professional in a monitored setting. Prepare the affected area by pretreating it with a local anesthetic cream; then apply the patch and leave it in place for 1 hour. As many as 4 patches can be used at once. A single application can provide pain relief for as long as 12 weeks. Adverse effects are mostly mild and transient.

In a double-blind, randomized, placebo-controlled trial with an open-label extension, the score on a numeric pain-rating scale declined from baseline in both the high-concentration capsaicin group and the placebo group during Week 1; however, the capsaicin-treated group experienced long-term improvement through Week 12.<sup>34</sup>

(See TABLE 1<sup>14-21, 23, 24, 27-34</sup> for a summary of pharmacotherapeutic options.)

### Alternative modalities to reduce pain

Acupuncture and transcutaneous electrical nerve stimulation (TENS) have been tried for the relief of PHN without consistent evidence of efficacy. There are no significant adverse effects associated with these therapies; however, the cost of treatment may be an issue. Acupuncture is not covered by many insurance carriers. Mental-health interventions, including cognitive and behavioral therapy, might help with overall physical and emotional functioning and quality of life.

### Invasive interventions

Researchers have examined several interventional modalities for treating PHN that is refractory to medication.

**Sympathetic nerve blocks.** Retrospective studies have shown that sympathetic nerve block provides short-term improvement in pain in 40% to 50% of patients with PHN.<sup>35</sup>

**Intercostal nerve block** has been reported to provide long-lasting pain relief in patients with thoracic PHN.<sup>36</sup>

**Neuraxial use** of intrathecal methylprednisone is supported by moderately good evidence

**TABLE 1****Pharmacotherapeutic options for managing postherpetic neuralgia<sup>14-21, 23, 24, 27-34</sup>**

Medication	Starting dose	Dose titration	Common adverse effects	Cautions and comments
<b>Anticonvulsants</b>				
Gabapentin	100-300 mg	Start at bedtime and increase to tid dosing; increase by 100-300 mg every 3-5 days to total dose of 1800-3600 mg/d in 3 or 4 divided doses	Somnolence, dizziness, fatigue, ataxia, peripheral edema, weight gain, visual adverse effects	Decrease dose in patients with renal impairment Dialysis patients: Every-other-day dosing; dosed on the day of dialysis Avoid sudden discontinuation
Extended-release gabapentin	600 mg daily for 3 days, then 600 mg bid beginning Day 4	600 mg bid	Somnolence, dizziness	Recently approved by FDA for PHN; not much clinical experience as yet
Pregabalin	50 mg tid or 75 mg bid	300-600 mg/d in 2 divided doses for 7-10 days	Somnolence, fatigue, dizziness, peripheral edema and weight gain, blurred vision, and euphoria	Decrease dose in patients with renal impairment Titrate dosage slowly in elderly patients
<b>Tricyclic antidepressants*</b>				
Amitriptyline Desipramine Nortriptyline	10-25 mg at bedtime. Start at a lower dose in elderly	Increase as tolerated every 2 weeks, with a target dose of 75-150 mg as a single daily dose	Sedation, dry mouth, blurred vision, weight gain, urinary retention, constipation, sexual dysfunction	Cardiac arrhythmic disease, glaucoma, suicide risk, seizure disorder Risk of serotonin syndrome with concomitant use of tramadol, SSRIs, or SNRIs Amitriptyline has the most anticholinergic effects
<b>Opioids</b>				
Fentanyl patch <sup>†</sup> Methadone <sup>‡</sup> Morphine Oxycodone	12 µg/hour 2.5 mg tid 15 mg q 6 hours prn 5 mg q 6 hours prn	Titrate at weekly intervals balancing analgesia and adverse effects. If patient tolerates the medications, can titrate faster	Nausea and vomiting, constipation, sedation, itching, risk of tolerance and abuse	Driving impairment and cognitive dysfunction during treatment initiation Be careful in patients with sleep apnea Additive effects of sedation with neuromodulating medications
<b>Atypical opioids</b>				
Tapentadol <sup>§</sup>	50 mg every 4-6 hours prn	Can titrate up to 100 mg q 4 hours. Maximum daily dose is 600 mg	Nausea and vomiting, constipation, drowsiness, and dizziness	Be careful in patients taking SSRIs, SNRIs, MAOIs, and TCAs Decrease dose in patients with moderate hepatic and renal impairment Avoid use in patients with a history of seizures
Tramadol	50 mg every 6 hours prn	Can titrate up to 100 mg q 6 hours. Maximum daily dose: 400 mg. Extended-release dosing once a day	Nausea and vomiting, constipation, drowsiness, dizziness	Be careful in patients with seizure disorder and concomitant use of SSRIs, SNRIs, and TCAs Decrease dose in patients with hepatic or renal disease
<b>Topical agents</b>				
Lidocaine patch	5% lidocaine patch	Can use up to 3 patches 12 hours/d	Local erythema, rash, blisters	Contraindicated in patients with known hypersensitivity to amide local anesthetics (eg, bupivacaine, mepivacaine) Do not use on skin with open lesions
Topical capsaicin	0.025% and 0.075% cream	Apply 3-4 times a day over affected region	No systemic adverse effects Burning and stinging sensation at the application site	Avoid contact with eyes, nose, and mouth Application of lidocaine gel locally may be helpful prior to capsaicin cream application
Capsaicin patch <sup>  </sup>	8% single application patch	Need topical local anesthetic application prior to patch application. Patch applied for 1 hour	Local site irritation, burning, temporary increase in pain	Done in a physician's office under monitored circumstances Patient may need oral analgesics for a short period following application of the patch

\*Obtain baseline EKG in patients with history of cardiac disease.

<sup>†</sup>May need to start a patient on short-acting opioid medications before changing over to a fentanyl patch.

<sup>‡</sup>Has a long and unpredictable half-life, hence the need for extra caution in elderly patients.

<sup>§</sup>Has not been studied in neuropathic pain; found to be effective in PHN and other chronic pain conditions.

<sup>||</sup>Single application has been found to be effective for about 3 months.

MAOI, monoamine oxidase inhibitor; PHN, postherpetic neuralgia; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Many surgical interventions have been used to treat PHN, but none has a role in clinical practice.

of benefit in patients with intractable PHN.<sup>37</sup> Because this intervention poses significant risk of neurologic sequelae, we do not recommend that it be used in clinical practice.

**Spinal cord stimulation** was studied prospectively in a case series of 28 patients.<sup>38</sup> Long-term pain relief was obtained in 82%. Patients serve as their own controls by switching off the spinal cord stimulator and monitoring pain. Consider spinal cord stimulation for patients with well-established PHN that is refractory to conventional management.

**Cryotherapy** was used for facial neuralgia pain, without significant benefit.<sup>39</sup> Another trial showed short-term benefit in 11 of 14 patients who underwent cryotherapy of the intercostal nerves for thoracic PHN.<sup>40</sup>

**Botulinium toxin A injection.** An abstract presented at the February 2010 meeting of the American Academy of Pain Medicine described how subcutaneous injection of botulinium toxin A reduced pain in patients with PHN, compared with lidocaine and placebo injections. The pain relief was noted in 1 week and persisted for 90 days.<sup>41</sup>

**Surgery.** Many surgical interventions have been described and used to treat PHN, but none has a role in clinical practice.

### When should you refer to a pain management center?

Dermatomal pain that lasts for longer than 180 days after a herpes zoster rash can be considered "well-established PHN" to denote its refractory nature. As a primary care clinician, you can refer a patient with PHN to a pain management center at any stage of disease but especially when the:

- patient has a significant medical comorbidity and you think that he or she requires the services of a specialist to manage multimodal pharmacotherapy
- PHN pain is refractory to conventional treatment modalities
- patient needs an invasive intervention
- patient needs treatment with a high-dose capsaicin patch and you have not been trained to apply it.

### Preventing herpes zoster and PHN

Obviously, preventing PHN is closely tied to preventing herpes zoster. To help prevent herpes zoster:

- vaccinate children with varicella vaccine to prevent primary varicella infection<sup>42</sup>

- use varicella-zoster immunoglobulin, as recommended by the CDC's Advisory Committee on Immunization Practices (ACIP), in immunocompromised, seronegative patients who were exposed recently to a person with chickenpox or herpes zoster<sup>42</sup>
- administer the herpes zoster vaccine to patients 60 years and older, as recommended by ACIP.<sup>43</sup> The FDA recently approved use of this vaccine for people 50 through 59 years, but ACIP has not changed its recommendations.<sup>44</sup>

As we've discussed, herpes zoster vaccination, antiviral therapy, and aggressive pain control can reduce the incidence, severity, and duration of acute herpes zoster and PHN.

A large multicenter, randomized, placebo-controlled trial demonstrated that herpes zoster vaccine decreases the likelihood of developing herpes zoster in immunocompetent individuals 60 years and older.<sup>45</sup> The vaccine reduced the incidence of herpes zoster by 51.3%; reduced the burden of illness by 61.1%; and reduced the incidence of PHN by 66.5%.<sup>45</sup> The live, attenuated vaccine is contraindicated in children, pregnant women, and immunocompromised individuals.

The number needed to treat for herpes zoster vaccine is 175; that is, 1 case of herpes zoster is avoided for every 175 people vaccinated.<sup>1</sup>

### Newer tools mean a better outcome

We have improved our ability to diminish the incidence of herpes zoster and PHN and to manage postherpetic pain more effectively. These advances include the development of a herpes zoster vaccine; consensus that antiviral therapy and aggressive pain management can reduce the burden of PHN; identification of efficacious treatments for PHN; and recognition of PHN as a study model for neuropathic pain research.

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One case of herpes zoster is avoided for every 175 people vaccinated.