Treating Herpes Zoster and Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is the most frequent chronic complication of herpes zoster (shingles).¹ Herpes zoster (HZ) represents a reactivation of the varicella zoster virus (VZV), a ubiquitous, highly neurotropic, exclusively human α-herpesvirus. Primary infection causes varicella (chickenpox), after which VZV becomes latent in sensory ganglia along the entire neuraxis. With the decline in VZV-specific cell-mediated immunity in elderly and immunocompromised individuals, VZV reactivates to cause HZ, characterized by a painful maculopapular or vesicular rash in all or part of the skin territory innervated by a single dorsal root ganglion.² The most common site of HZ is thoracic, comprising about half of all cases, followed by trigeminal (usually the ophthalmic branch), cervical, and lumbar distributions. HZ generally resolves within a few weeks, but a minority of patients experience pain (PHN) persisting for months, years, or even a lifetime.

Epidemiology of HZ and PHN

According to a recent systematic review, the incidence of HZ is 3–5 cases per 1000 person-years.³ The age-specific incidence rates of HZ were similar across countries, with a steep rise after 50 years of age. The incidence was 6–8 cases/1000 person-years at 60 years of age and 8–12 cases/1000 person-years at 80 years of age. The incidence of HZ has increased in the past several decades across seven countries.³ A study in the United States could not explain the increase by changes in age or by the prevalence of immunocompromised people.⁴ Two-thirds of HZ cases occur in those 50 years or older, and the lifetime risk is 30%.² Estimates of the incidence of PHN vary widely depending on the population and the definition of PHN used. Definitions include the duration of persistent pain (30, 90, or 180 days) and the severity of pain, either clinically meaningful pain (i.e., pain intensity of at least 3/10) or any pain.³ In a population-based study using medical records in the United States, 18% of patients reported pain for at least 30 days and 10% for at least 90 days.⁵ Similarly, 20% of patients had pain for at least 30 days and 14% for at least 90 days in a study from the United Kingdom.⁵ and 20% of zoster patients had pain at 3 months and 15% had pain at 2 years in a Dutch study.⁶ In the landmark zoster vaccine study, which included almost 40,000 people aged 60 years or older (of whom fewer than 1000 developed HZ) and where PHN was defined as pain intensity of 3/10 or more, 30% of patients who developed HZ had PHN at 1 month, 12% at 3 months, and 5% at 6 months in the placebo group.⁷ According to a meta-analysis, incidence rates of PHN varied from 3.9 cases per 100,000 person-years to 42.0 cases per 100,000 person-years across all ages.⁸

PHN risk increases with age. In a study from the United States, the incidence of PHN (defined as pain at 3 months) in zoster patients was 18% in persons older than 50 years and 33% in those older than 80 years. Overall, 80% of all PHN occurs among persons aged 50 years and older.² Analysis of data from the United Kingdom General Practice Research Database showed that the incidence of PHN (as defined by pain at 3 months) rose from 8% at 50–54 years of age to 21% at 80–84 years of age.⁵

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Advancing age and the severity of acute HZ pain are the strongest risk factors for PHN. Other predictors of PHN are the severity of the rash, the presence of prodromal pain, and the occurrence of sensory abnormalities such as hypoesthesia or allodynia. Ophthalmic location of rash, psychosocial distress in the acute phase, and problems with usual activities before developing HZ (the last reflecting poorer health) are also reported as risk factors.

### Course of the Disease

HZ viral replication first manifests as ganglionitis and then spreads along the corresponding peripheral nerve and the skin. Hemorrhage and inflammation in the affected dorsal root ganglion and associated nerve may be seen, and in patients with PHN, fibrosis and cell loss have been documented post mortem in the dorsal root ganglion. Pain and unilateral rash are typical symptoms, often accompanied by paresthesias and itching. Most patients experience pain during HZ. Pain precedes rash in three-quarters of cases, lasting usually for some days before the eruption of the rash. As described above, only a minority of patients continue to have pain long after the healing of the rash.

HZ can also give rise to non-pain complications, which can be ophthalmic (e.g., keratitis or uveitis), neurological (e.g., cranial and peripheral nerve palsies), circulatory (vasculitis and stroke), dermatological (e.g., bacterial superinfection), or visceral (e.g., pneumonia).

Those who continue to suffer from prolonged pain after HZ may describe one or more of three broad types of pain: (1) a constant deep aching or burning pain; (2) an intermittent paroxysmal pain with a lancinating quality; and (3) an intermittent pain evoked by normally innocuous sensory stimuli (allodynia), typically mechanical but in some patients thermal as well. Allodynia is present in at least 70% of patients and is usually considered to be the most distressing and debilitating PHN component. Itching and dysesthesias may accompany the pain, and in some patients these symptoms can be even more annoying than the pain itself.

A longitudinal study of zoster patients using quantitative sensory testing (QST) and skin biopsies showed that those who developed PHN (defined as pain at 6 months) had significantly more impaired sensory function and more severe allodynia in the acute phase compared to those who experienced pain resolution. Sensory recovery proceeded at the same rate in both groups during the first 6 months. Epidermal nerve fiber density was decreased by about 40% in the affected skin but not in contralateral “mirror image” skin, with no improvement during the first 6 months. In a long-term follow-up of 7 years, epidermal nerve fiber density remained low in spite of good clinical recovery, which strongly supports the concept that recovery of sensory function and anatomical reinnervation of the skin are not prerequisites for pain resolution.

### Burden of the Disease

Pain is the most important outcome of HZ. It interferes with general activity, sleep, and mood, and patients with more severe pain are more likely to report symptoms of anxiety and depression. Health-related quality of life instruments measure four key health domains: physical, psychological, social, and functional. Both HZ and PHN have effects on patients’ lives across all four health domains. Reduced quality of life is a particular problem in patients whose pain persists as PHN, and there is a correlation between increasing pain severity and the extent of PHN’s negative impact on quality of life. A study comparing patients with PHN to patients with chronic low back pain showed similar pain intensity, physical function, cognitive function, and mood in both groups, but pain severity depended on different things (PHN typically increased with touch, air movement, and stress, whereas low back pain increased with activity and exercise).

Hz and PHN also cause a substantial economic burden to society in the form of increased health care use and need for medication, lost working days in those at working age, and the need for assistance or even loss of independence in frail, elderly, people with multiple comorbidities. In a study from the United Kingdom, the average total cost of a PHN case was estimated to be £340 in 2006. The cost included outpatient visits and prescribed medication, but at that time pregabalin and lidocaine patches were not available there, which would increase the current cost.

### Pharmacotherapy of Acute Herpes Zoster

The treatment of HZ aims to limit the duration and severity of the attack, relieve symptoms, and prevent complications. All patients should receive a medical and psychosocial history evaluation and targeted physical examination to confirm the diagnosis, document comorbid illnesses, and provide a basis for treatment.

### Antiviral Agents

Although HZ is a self-limiting and benign disease in most patients, those who have a high risk of developing complications should be treated actively. Systemic antiviral therapy is strongly recommended as first-line treatment for all immunocompetent patients with HZ who fulfill any of the following criteria (ideally within 72 hours of the onset of rash): (1) are at least 50 years of age; (2) have moderate or severe pain; (3) have a moderate or severe rash; or (4) have non-truncal involvement.

Acyclovir, famciclovir, and valacyclovir have been approved by the U.S. Food and Drug Administration for the treatment of HZ. All of them inhibit viral replication in the infected cells, resulting in accelerated healing of rash and decreased severity and duration of acute pain. Oral acyclovir does not reduce the incidence of PHN significantly, but there is insufficient evidence to determine the effect of other antiviral treatments preventing PHN.
Treatment of Acute Zoster-Associated Pain

Active treatment of acute HZ pain is recommended. In the absence of an extensive dataset of direct evidence from high-quality randomized controlled trials, it is reasonable to adhere to generic principles of acute pain management; patients with mild to moderate pain should take acetaminophen (paracetamol) or NSAIDs, alone or in combination with codeine or tramadol. Those with severe pain may need a strong opioid. In a randomized controlled study, the number-needed-to-treat for clinically meaningful pain relief (>30% pain reduction) was 2.9 for controlled-release oxycodone and 9.6 for gabapentin during the 4-week study. In another study, a single dose (900 mg) of gabapentin decreased pain severity and both severity and area of allosthesia in patients with acute zoster. For opioids, individual titration, routine laxative use, and close follow-up are needed to ensure the best compromise between efficacy and side effects.

Low-dose amitriptyline (25 mg once daily for 3 months) has been recommended because it significantly reduced the prevalence of PHN at 6 months in a placebo-controlled trial. However, this small study requires repetition on a larger scale.

Corticosteroids in combination with acyclovir reduced pain and improved short-term quality of life compared with placebo in patients with HZ, but they had no appreciable effect on the incidence or duration of PHN. Corticosteroids are associated with a considerable number of adverse effects and hence should be used only in patients with severe symptoms at presentation or in whom no major contraindications to corticosteroids exist, and only in combination with antiviral treatment.

Although epidural local anesthetic injection, with or without a steroid, has been common practice for many decades in patients with severe acute or subacute zoster pain, there are few prospective controlled trials. A large study that examined the effect of a single epidural injection of local anesthetic and a steroid demonstrated reduced zoster-associated pain at 1 month but no significant reduction in the likelihood of PHN. A randomized nonblinded study reported effective pain relief and prevention of PHN (defined as presence of any pain) at 1.6, and 12 months with repeated paravertebral blockades of a local anesthetic and steroid. All patients (aged 50 years or over) were treated with oral acyclovir, and the paravertebral blockade group received four repeated treatments within one week, whereas the standard group received simple analgesics for their pain. According to this study, repeated paravertebral blockades are effective for acute pain and prevention of PHN. However, this procedure is obviously not suitable for patients suffering from cranial zoster.

Treatment of Postherpetic Neuralgia

The efficacy of current treatments is still far from satisfactory. PHN is a classical model to test the efficacy of potential new drugs for neuropathic pain. A global database of all registered PHN trials and results (if any are available) has been reported and was updated in mid-2014. The database is available as part the Repository of Registered Analgesic Clinical Trials (RReACT) through the ACTTION website (http://www.ctionline.org/). Of 112 unique registered trials, 66 were reported as completed. Only 20 completed trials had results available in the peer-reviewed literature, and another 17 had results available via the “gray” literature or posted on a trials registry. In addition to the lack of results from a large proportion of completed trials, some important clinical issues have not been tested in a clinical trial. For example, none of the available serotonin and norepinephrine reuptake inhibitors (SNRIs) have been studied for PHN.

Numerous meta-analyses and treatment guidelines have been published. A PHN-specific meta-analysis was published in 2005, but recommendations provided here are largely based on analyses from 2014 and 2015. Tricyclic antidepressants (TCAs), gabapentinoids, opioids, and topical capsaicin have strong evidence.
for efficacy in PHN (Table 1). Topical lidocaine gel (5% in a nonstandard formulation) for PHN showed efficacy in a double-blind, three-session study, as did topical lidocaine patch (5%) in a double-blind, four-session study. In an open-label, non-inferiority study, 5% lidocaine patch showed better efficacy compared with pregabalin in patients with PHN.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug, Maximal Daily Dose</th>
<th>Outcome</th>
<th>Number Randomized</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td><strong>TCAs</strong></td>
<td></td>
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<tr>
<td>Watson et al. 1982</td>
<td>Amitriptyline, average 73 mg</td>
<td>P</td>
<td>24</td>
<td>3 weeks</td>
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<tr>
<td>Max et al. 1988</td>
<td>Amitriptyline, average 65 mg</td>
<td>P</td>
<td>62</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Graff-Radford et al. 2000</td>
<td>Amitriptyline, 200 mg</td>
<td>NA</td>
<td>24/49</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Kishore-Kumar et al. 1990</td>
<td>Desipramine, 250 mg</td>
<td>P</td>
<td>26</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Raja et al. 2002</td>
<td>Nortriptyline or desipramine, 160 mg</td>
<td>P</td>
<td>76</td>
<td>8 weeks</td>
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<tr>
<td><strong>PREGABALIN</strong></td>
<td></td>
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<tr>
<td>Dworkin et al. 2003</td>
<td>Pregabalin, 600 mg</td>
<td>P</td>
<td>173</td>
<td>8 weeks</td>
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<tr>
<td>Sabatowski et al. 2004</td>
<td>Pregabalin, (150), 300 mg</td>
<td>P</td>
<td>157/238</td>
<td>8 weeks</td>
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<tr>
<td>van Seventer et al. 2006</td>
<td>Pregabalin, (150), 300, 600 mg</td>
<td>P</td>
<td>281/370</td>
<td>13 weeks</td>
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<tr>
<td>Stacey et al. 2008</td>
<td>Pregabalin, 300, 600 mg</td>
<td>P</td>
<td>270</td>
<td>4 weeks</td>
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<tr>
<td><strong>GABAPENTIN</strong></td>
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<tr>
<td>Rowbotham et al. 1998</td>
<td>Gabapentin, 3600 mg</td>
<td>P</td>
<td>229</td>
<td>8 weeks</td>
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<tr>
<td>Rice and Maton 2001</td>
<td>Gabapentin, 1800, 2400 mg</td>
<td>P</td>
<td>334</td>
<td>7 weeks</td>
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<tr>
<td><strong>GABAPENTIN ER or ENACARBIL</strong></td>
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<tr>
<td>Wallace et al. 2010</td>
<td>Gabapentin ER, 1800 mg</td>
<td>N</td>
<td>407</td>
<td>10 weeks</td>
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<tr>
<td>Sang et al. 2012</td>
<td>Gabapentin ER, 1800 mg</td>
<td>P</td>
<td>452</td>
<td>10 weeks</td>
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<tr>
<td>Irving et al. 2009</td>
<td>Gabapentine ER, 1800 mg</td>
<td>P twice daily; N once daily</td>
<td>158</td>
<td>4 weeks</td>
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<tr>
<td>NCT00619476 ClinTrials.gov</td>
<td>Gabapentin enacarbil, 1200, 2400, 3600 mg</td>
<td>P</td>
<td>376</td>
<td>13 weeks</td>
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<tr>
<td><strong>TRAMADOL</strong></td>
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<tr>
<td>Boureau et al. 2003</td>
<td>Tramadol, 400 mg</td>
<td>P</td>
<td>127</td>
<td>6 weeks</td>
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<tr>
<td><strong>OPIOIDS</strong></td>
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<tr>
<td>Watson and Babul 1998</td>
<td>Oxycodone, 60 mg</td>
<td>P</td>
<td>50</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Raja et al. 2002</td>
<td>Morphine, 240 mg, or methadone</td>
<td>P</td>
<td>76</td>
<td>8 weeks</td>
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<tr>
<td><strong>CAPSAICIN 8%</strong></td>
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<tr>
<td>Backonja et al. 2008</td>
<td>Capsaicin, 8%, single application</td>
<td>P</td>
<td>402</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Backonja et al. 2010</td>
<td>Capsaicin, 8%, single application</td>
<td>P</td>
<td>38</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Irving et al. 2011</td>
<td>Capsaicin, 8%, single application</td>
<td>P</td>
<td>418</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Webster et al. 2010</td>
<td>Capsaicin, 8%, single application</td>
<td>P</td>
<td>299</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Webster et al. 2010</td>
<td>Capsaicin, 8%, single application</td>
<td>N</td>
<td>155</td>
<td>12 weeks</td>
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<tr>
<td><strong>CAPSAICIN CREAM</strong></td>
<td></td>
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<tr>
<td>Bernstein et al. 1989</td>
<td>Capsaicin, 0.075%</td>
<td>P</td>
<td>32</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Watson et al. 1993</td>
<td>Capsaicin, 0.075%</td>
<td>P</td>
<td>143</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

Source: Data from supplementary material of Finnerup et al. Abbreviations: ER, extended release; NA, not applicable; TCAs, tricyclic antidepressants.

First-Line Agents According to the NeuPSIG Guidelines

The lack of evidence for different efficacies for most drugs in distinct neuropathic pain disorders caused NeuPSIG...
to prepare recommendations for neuropathic pain in general instead of for various etiologies. First-line agents for neuropathic pain are TCAs, SNRIs, and gabapentinoids on the basis of evidence of their efficacy and safety. However, there are no published reports of randomized controlled clinical trials of any of the SNRIs in PHN patients. Table 2 presents the mechanisms of action and dosing for these drugs.

**TCAs** are inexpensive drugs. The presence of depression is not required for their analgesic effect, and pain relief occurs with lower doses than are required for an effect on mood. The most common side effects of TCAs include sedation, anticholinergic effects (e.g., dry mouth, constipation, and urinary retention), and orthostatic hypotension. In a head-to-head comparison, amitriptyline and nortriptyline were equally effective, but nortriptyline was better tolerated. These drugs are contraindicated in patients with cardiac conduction problems or recent myocardial infarction. Patients may complain of excessive sedation or confusion as the most troublesome side effect, and pre-existing cognitive impairment may become significantly worse, which may require a cautionary approach to driving. Accidental or intentional overdose with a TCA may be lethal, and is more dangerous compared to SSRI antidepressants.

**Gabapentinoids** (gabapentin and pregabalin) have been studied extensively for PHN (Table 1). Their advantage is lack of pharmacokinetic interactions, as they are not bound to plasma proteins and are secreted to urine without hepatic metabolism. Gabapentin has a saturable transport mechanism in the gut, whereas absorption of pregabalin is more linear. The typical side effects of gabapentinoids are somnolence, dizziness, and peripheral edema. Doses must be adjusted downward if renal function is impaired. Gabapentin is dosed differently depending on the preparation. Neurontin and generic gabapentin differ from the gabapentin extended-release (Gralise) preparation and the gabapentin enacarbil prodrug (Horizant) (see each manufacturer’s recommendations).

### Table 2

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Starting Dose</th>
<th>Titration</th>
<th>Maximum Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCAs</strong></td>
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</tr>
<tr>
<td>Nortriptyline, desipramine, (amitriptyline, imipramine)¹</td>
<td>Serotonin and norepinephrine reuptake inhibition, sodium channel block, NMDA-receptor antagonism</td>
<td>10–25 mg at bedtime</td>
<td>Increase by 10–25 mg every 3–7 days as tolerated</td>
<td>Usual effective doses in 75–100 mg/day range. Upward titration from 75 mg/day guided by blood concentration of the drug and its active metabolite. Pretreatment cardiac conduction screening in older patients and re-screening as the dose rises may be indicated. Do not exceed 150 mg daily.</td>
</tr>
<tr>
<td><strong>Gabapentinoids</strong></td>
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<tr>
<td>Gabapentin</td>
<td>Calcium-channel α₂δ binding, which reduces release of presynaptic transmitters</td>
<td>100–300 mg at bedtime</td>
<td>Increase by 100–300 mg three times daily every 1–7 days</td>
<td>3600 mg daily (divided into 3 doses)</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Calcium-channel α₂δ binding, which reduces release of presynaptic transmitters</td>
<td>75 mg twice daily</td>
<td>Increase to 300 mg daily after 3–7 days, then by 150 mg/d every 3–7 days</td>
<td>600 mg daily (divided into 2–3 doses)</td>
</tr>
<tr>
<td><strong>Opioid Agonists</strong></td>
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<tr>
<td>Tramadol</td>
<td>µ-opioid receptor binding and serotonin and norepinephrine reuptake inhibition</td>
<td>50 mg once or twice daily</td>
<td>Increase by 50–100 mg daily in divided doses every 3–7 days as tolerated</td>
<td>400 mg daily; in patients older than 75, 300 mg daily</td>
</tr>
<tr>
<td>Oxycodone CR</td>
<td>µ-opioid receptor binding</td>
<td>10 mg twice daily</td>
<td>Increase by 20 mg daily or more slowly as tolerated</td>
<td>120 mg daily (divided into 2 doses)²</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR, controlled release; TCAs, tricyclic antidepressants.

1 Secondary amine TCAs (nortriptyline, desipramine) are preferred owing to better tolerability.

2 Highest dose used in randomized controlled studies for neuropathic pain.
Second-Line Agents According to the NeuPSIG Guidelines

Lidocaine patches (5%), capsaicin patches (8%), and tramadol are recommended as a second line of treatment. The reason for their being second-line is a low quality of evidence (lidocaine), a relatively small effect size (topical capsaicin), or lower tolerability or safety (tramadol).

Topical lidocaine blocks voltage-dependent sodium channels in the area of application. Lidocaine patches (a maximum of three patches) are applied to the region of pain once a day for up to 12 hours. For old and frail patients and for those with concerns about the side effects or safety of first-line treatments, lidocaine patches might be a first-line option. If lidocaine patch is not available, lidocaine gel or cream (5%) can be tried instead (dosing three times daily), although alternate preparations have not been tested for efficacy in a clinical trial.

Topical capsaicin is an agonist of the TRPV1 ion channel and binds its receptors, which are expressed by nociceptive primary sensory neurons, causing excitation of neurons and a period of enhanced sensitivity perceived as itching, pricking, or burning, with cutaneous vasodilatation. This phase is followed by persistent desensitization. A high-concentration capsaicin plaster (8%) has shown efficacy in clinical trials as a single treatment applied to the painful area for 60 minutes by a medical professional. The treatment can be repeated in every 3 months, if needed.

Tramadol has good evidence of efficacy and a lower potential for misuse, abuse, and dependency compared to strong opioids, but it is recommended as a second-line drug owing to potential safety concerns. It exerts its analgesic action by increasing noradrenergic and serotonergic neurotransmission in the central nervous system. The parent compound is demethylated to an active metabolite, trans-O-desmethyltramadol, by the CYP2D6 enzyme. This biotransformation is a prerequisite for the clinical opioid effect of tramadol. “Poor metabolizers” lack this bioactivation, and they have a weaker analgesic response to tramadol compared to “extensive metabolizers” and “ultra-rapid metabolizers.” The typical side effects of tramadol are nausea, dizziness, sedation, and headache. Tramadol should be used with caution with concomitant antidepressant medication owing to its interaction potential.

Third-Line Agents According to the NeuPSIG Guidelines

Strong opioids (particularly oxycodone and morphine) and botulinum toxin A are recommended as third line mainly because of safety concerns (opioids) or weak quality of evidence (botulinum toxin A). Strong opioids (oxycodone, morphine, and methadone) have shown efficacy in PHN. Typical side effects are constipation, nausea, itching, and sweating. Opioids are recommended as a third-line option owing to their abuse potential and side effects, including endocrine effects. Long-term opioid treatment should be considered for nonmalignant pain only when other relevant treatment options have been tried. Psychosocial evaluation should precede commencement of opioid treatment. After a treatment trial, the achieved beneficial effects (pain relief and improved function) are weighed against adverse drug reactions. Slow-release formulations are preferred.

Botulinum toxin has been studied for PHN in two randomized controlled trials with positive results. Currently this treatment is recommended only for specialist use in refractory cases.

Combination Therapy

Few studies of drug combinations have been published, even though combination therapy reflects actual clinical practice. Randomized trials suggest that the combination of pregabalin or gabapentin and duloxetine or tricyclic antidepressants is an alternative option to increasing doses of one class of drugs for patients unresponsive to moderate doses of monotherapy. As multiple pain mechanisms coexist in PHN, combining drugs with different mechanisms of action is rational and should be studied further to better understand its value in the clinic.

Combining a locally acting preparation (lidocaine or capsaicin) with a systemic drug is reasonable and should be tried, especially for those with comorbidities and multiple medications, to reduce the risk of interactions of systemic drugs.

Drugs Not Recommended by NeuPSIG

The recommendations for tapentadol, other antiepileptics, capsaicin cream, topical clonidine, selective serotonin reuptake inhibitor antidepressants, and NMDA antagonists are inconclusive, mainly because of discrepant findings. Cannabinoids and valproate have weak recommendations against their use in neuropathic pain, and levetiracetam and mexiletine have strong recommendations against their use because of generally negative trials or safety concerns, or both.

Role of Invasive Treatments for Postherpetic Neuralgia

A recent comprehensive review on interventional management of neuropathic pain concluded that owing to the low quality of the available evidence and the potential for adverse events, the role of spinal cord stimulation, deep brain stimulation, and intrathecal medication delivery is inconclusive in PHN. The authors recommended against sympathetic blocks for PHN because nonrandomized studies have not shown benefit and there are no well-controlled prospective clinical trials.

A randomized controlled study appeared to demonstrate efficacy over 1–2 years for four intrathecal injections of methylprednisolone performed over 1 month compared with lidocaine alone and with a no-treatment control group. Another group attempted to replicate the findings, but the trial was terminated early after all six patients randomized to intrathecal methylprednisolone experienced an increase in pain at 8 weeks (compared to one of four participants in the control group).

Given the failure to replicate the striking result of the first study and the potential risks of intrathecal methylprednisolone injections, the role of this treatment remains inconclusive, and we strongly recommend against its use.
Prevention of Postherpetic Neuralgia
The only well-documented means of preventing PHN is the prevention of HZ. A live attenuated VZV vaccine is approved for immunocompetent persons of age 50 years or older. The Shingles Prevention Study, which included people 60 years or older, showed that the vaccine reduced the incidence of HZ by 51% and the incidence of PHN by 66%. A smaller study involving persons 50 to 59 years of age showed that vaccination reduced the incidence of HZ by 70%. A long-term persistence substudy showed that vaccine efficacy decreased from 51% to 21% for incidence of HZ and from 66% to 35% for incidence of PHN from 7 through 11 years post-vaccination. Statistically significant vaccine efficacy for incidence of HZ persisted only through year 8. Cost-effectiveness analyses of the zoster vaccine have estimated the cost of a quality-adjusted life year from US$10,000 to more than US$100,000 depending on assumptions regarding duration of vaccine protection and the magnitude of the loss in quality of life associated with HZ and PHN. In the United Kingdom, researchers estimated that vaccination at either 65 or 70 years is the most cost-effective, whereas a German study concluded that vaccinating individuals aged 60 years seems to represent the most cost-effective vaccination strategy. Future cost-effectiveness analyses should also incorporate the employment-related productivity loss in addition to health care costs and lost quality of life.

Conclusion
HZ and PHN present challenges to health care systems, as they are prevalent, cause suffering and impaired function, and are difficult to treat satisfactorily, especially in societies with aging populations. The optimal use of the current therapies by tailoring the treatment individually, monitoring the patients to assess efficacy, tolerability, and functional status, and providing support in psychosocial aspects when needed may improve the results. Zoster vaccine is available to prevent zoster, and new compounds to treat PHN are awaited.

Conflicts of Interest
Maija Haanpää has been a member of the advisory boards of Abbvie, Allergan, Astellas, Eli Lilly, Janssen Cilag, Pfizer, and Sanofi-Aventis. International congress attendance (registration fees, travel costs, accommodation) has been financially supported by Astellas and Pfizer. Lecture fees related with lectures at seminars or symposia are paid by Astellas, Eli Lilly, Janssen Cilag, MSD, Mundipharma, Orion, Pfizer, and Sanofi-Pasteur MSD.

Andrew Rice is a member of varicella zoster the Joint Committee on Vaccination and Immunisation (JCVI), which advises U.K. health departments on immunization. He is a member of the scientific advisory board of Spinifex Pharmaceuticals and holds share options in the company. Through Imperial College Consultants, he has in the past 24 months provide consultancy services from Spinifex, Relanda, Neusentis, Astellas, Abide, Aquilas, Mitsubishi, Medivir, and Asahi Kasei Pharma. His laboratory has within the last 24 months received research funding from Pfizer and Astellas.

Michael Rowbotham has served as a consultant to Xenoport, Lilly, Chromocell, Signature Therapeutics, ViroBay, and Nektar. He holds stock or stock options in Xenoport, Affrent, Signature Therapeutics, VistaGen, and Centrexion.

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