Post-herpetic neuralgia

Rajesh Gupta MD FRCA
Paul Farquhar Smith MA MB BChir FRCA PhD FFPMRCA FFICM

Key points
Post-herpetic neuralgia is chronic pain 3 months after herpes zoster.
Risk factors include old age, female sex, more intense acute pain, severe rash development, and a prodrome of dermatomal pain before the rash.
Clinical features include pain, numbness, itch, and skin pigmentation.
Prevention is an important component of management and includes zoster vaccine and antiviral agents.
Treatment consists of a multimodal approach with gabapentinoids, tricyclic antidepressants, and possibly topical lidocaine as first-line treatments.

Post-herpetic neuralgia (PHN) is defined as chronic pain (>3 months) with skin changes in the distribution of one or more sensory roots subsequent to herpes zoster infection. However, the variation in time scale describing persistent pain from 1 month after herpes zoster to 3–6 months after the rash onset or, in some cases, after the rash has resolved makes it difficult to compare the studies of PHN.

Herpes zoster, also known as shingles, results from the reactivation of varicella zoster virus (VZV), a double-stranded DNA herpes virus, which persists in a clinically latent state in spinal and cranial sensory ganglia after primary infection with varicella (chickenpox).

Cell-mediated immunity normally prevents viral reactivation, and immunity is increased by varicella immunization of children (exogenous boosting) and by exposure to wild-type virus after primary infection (endogenous boosting). Immunity may decrease below a threshold and virus reactivation may result because of:

- Disease, for example, lymphoma and human immunodeficiency virus
- Immune suppression, for example, after organ transplant and autoimmune disease
- Management of malignancy, for example, radiotherapy, chemotherapy

About 20% of the patients with herpes zoster develop PHN.

Pathophysiology of pain

Pathological findings include the degeneration of affected primary afferent neuronal cell bodies and axons, the atrophy of the spinal cord dorsal horn, the scarring of the dorsal root ganglion, and the loss of epidermal innervation. In a subset of PHN patients, there is a complete loss of both large and small diameter sensory afferent fibres. This loss of peripheral input results in the development of spontaneous discharges in the deafferentated central neurones, leading to intrinsic changes in the central nervous system (CNS). This produces constant pain in addition to mechanical allodynia in the area of sensory loss. Apart from continuous pain, paroxysms of pain are seen due to high-frequency discharges of impulses abnormally generated in demyelinated Aδ fibres. Both sensitization and deafferentation play a role in the genesis of pain. Virus spreads from the nerve root to the corresponding dermatome and causes inflammation and neural injury, leading to peripheral sensitization and resulting in increased afferent input to the spinal cord. Sensitization of intact C nociceptor fibres leads to allodynia and reduced thermal sensory threshold. Spontaneous burning pain is also common in these patients. Central sensitization may result from sprouting of Aβ fibres centrally in response to partial loss of C-fibre input. Regenerating Aβ fibres make contact with those central receptors that previously received input from the C-fibres, resulting in the development of tactile allodynia and hyperalgesia. However, there is speculation whether these processes occur in humans.

PHN patients may be subgrouped into three types based on distinct underlying pain pathophysiology:

- Irritable nociceptors
- Deafferentation with alldynia
- Deafferentation without alldynia

Irritable nociceptors develop secondarily to abnormally functioning primary afferent neurones that generate and maintain pain. Patients with deafferentation-type pain with alldynia often describe profound sensory loss in the area of greatest pain. The sensory loss is predominantly thermal but dynamic mechanical allodynia (pain on brushing) is often present. Allodynia may be related to spouting of Aβ primary afferents into areas of the dorsal horn that have lost their normal pain fibre input. Finally, deafferentation-type pain without alldynia is believed to be maintained by CNS secondary sensitization of dorsal horn neurones. Alldynia is not present because there is a complete primary afferent neurone disconnection. Quantitative sensory testing shows predominantly hyperalgesia and the loss of pin prick sensation.
Risk factors

Risk factors for PHN in patients with herpes zoster include older age, female sex, more intense acute pain, more severe rash developing within 3 days after the onset of herpes zoster, and a prodrome of dermatomal pain before the rash appears especially if associated with fever (>38°C).

The presence of a prodrome may reflect early viral damage in the affected sensory ganglion. Rash severity may be related to greater damage to and loss of epidermal nerve fibres. Severe acute pain probably enhances central sensitization and excitotoxic damage in the dorsal horn.

PHN is rare in younger subjects (<50 yr), and incidence rises sharply after the age of 60. Older age may be a risk factor because of the association of subclinical polyneuropathy. Compromised nerve fibres need less viral damage to cause PHN. Ageing is also associated with the degeneration of myelinated afferent fibres adding to their susceptibility to viral damage.

The incidence of PHN is also likely to be increased in women because of their longer average life expectancy compared with men (80.0 vs 74.8 yr). Women are also more likely to report more severe pain and pain of longer duration than men.4

Psychosocial predictors have been suggested with those having anxiety, and poor coping strategies to stress are more likely to develop significant pain.

Natural history and clinical presentation

Herpes zoster pain may be divided into acute pain lasting 30 days, subacute (30–120 days), or chronic from 3 months after rash healing or 4 months after the start of the prodrome (although there are variable definitions). Many patients describe prodromal pain where skin lesions subsequently appear. The prodrome lasts 2–3 days but may extend to more than a week. The prodrome is the time period taken by the virus to replicate and cause necrosis and inflammation in the dermatomal skin. PHN most commonly involves thoracic dermatomes, although in 20% of the patients, the ophthalmic division of the trigeminal nerve is involved.

In some patients, pain does not resolve after the subacute phase but continues for months or years as PHN. Rarely, pain can occur without any evidence of rash. Pain can be continuous or intermittent and deep or superficial, and the nature of the pain is variable and described as ‘throbbing’ or ‘burning’. The pain intensity characteristically increases during the day and is worse at night or when tired or stressed. Allodynia is frequently experienced and causes severe patient distress. Patients may become isolated, depressed, or anxious due to the unrelieved pain and the inability to wear clothing over the involved region. Patients may experience various symptoms such as weight loss, chronic fatigue, anorexia, and decreased physical activity. Interference with sleep is one of the most common problems. Depression and concentration deficit may accompany.

Some patients report sensory deficit or itch, while others report skin pigmentation or scarring after the rash. Motor weakness, including loss of muscle tone, may be present and may be associated with autonomic dysfunction (e.g. abnormal skin temperature, colour, and sweating).

Over half of the patients with PHN of more than 3 months duration show significant improvement in pain at 6 months. More than half will be on no treatment, but some will follow a progressive course and develop significant pain despite initial improvement.

Management of PHN

The management of PHN includes the prevention of initial infection and the aggressive management of the acute phase of herpes zoster. However, as for any type of chronic pain, a multimodal approach to treatment should be used for patients afflicted with PHN.

Prevention

The main therapies for PHN prevention include primary varicella vaccine, zoster vaccine, and antiviral medications.

Primary varicella vaccine given in childhood reduces the incidence of chicken pox and subsequent herpes zoster and PHN. The vaccine virus is less likely to establish latency and reactivate than the wild-type VZV. Zoster vaccine given to older adults boosts waning immunity. A live attenuated VZV vaccine using the Oka/Merck strain has been shown to decrease the incidence of herpes zoster, decrease the overall burden of illness, and decrease the incidence of PHN.5

Antiviral drugs (acyclovir, valaciclovir, and famciclovir) control viral DNA replication, reduce acute pain severity and duration, hasten rash healing, and shorten the period of viral shedding.6 The number of patients with pain at 6 months may be approximately halved. The addition of oral steroids to acyclovir improves acute pain management and allows quicker return to normal activities of daily life and sleep patterns compared with acyclovir alone. However, the combination does not appear to prevent PHN.

All immunocompromised patients, those over 50 yr, and those with ophthalmic involvement should be given antiviral treatment. They are also indicated for patients less than 50 yr with severe acute pain and/or rash. Anticonvulsants and antidepressants have been tried for the prevention of PHN. Amitriptyline started within 48 h of the onset of rash has shown a 50% decrease in pain prevalence at 6 months, but the study was not replicated.

Clinical treatment

Systematic reviews and meta-analyses have shown evidence of analgesic efficacy as first line for gabapentinoids (pregabalin,
Gabapentin, tricyclic antidepressants (TCAs), and topical lidocaine. Number needed to treat (NNT) and number needed to harm (NNH) will be stated where sufficient dichotomous data were available in systematic review to calculate them.8

Anticonvulsants

Gabapentinoids are structurally similar to γ-aminobutyric acid and act at the α3δ-subunit of presynaptic voltage-dependent calcium channels on primary nociceptors. Their action decreases calcium influx, thus reducing the release of the excitatory transmitter glutamate. There is evidence for the efficacy of gabapentin in not only PHN but also other types of neuropathic pain. One proposed dose regimen is a single 300 mg dose on days 1 and 2, increasing to 600 mg day⁻¹ on days 3 and 4 and then to 900 mg day⁻¹. Further increase in dosage should be gradual over a period of weeks up to a daily dose of 1800 mg day⁻¹. Dose may be increased further up to the maximum daily licensed dose of 3600 mg. Indeed, some of the efficacy data from a randomized controlled trial (RCT) used doses up to 3600 mg day⁻¹. The most common adverse events reported include dizziness, drowsiness, weakness, peripheral oedema, dry mouth, diarrhoea, and gait problems. A systematic review calculated the NNH for minor side-effects as 4 and 12.2 for major side-effects.9

Pregabalin is similar in efficacy to gabapentin as denoted by their similar NNTs (4.39 and 4.93 for gabapentin and pregabalin, respectively). The onset of pain relief is said to be quicker which potentially allows a quicker titration when compared with gabapentin. The posology of pregabalin is twice-daily dosing compared with three times a day with gabapentin.

The side-effect profile is similar for the two gabapentinoids and the most commonly reported adverse effects are dizziness, somnolence, gait problems, and mild peripheral oedema. When pregabalin was used for PHN, the NNH for minor side-effects (taken from a single RCT) was 4.27 and for major harm ranged from 4.86 to 27.5. There is some evidence of efficacy for other anticonvulsants. One small RCT (n=48) has shown efficacy for sodium valproate.

Antidepressants

The TCAs derive their name from its structure of two aromatic rings attached to a cycloheptane ring. TCAs (amitriptyline, desipramine, and nortriptyline) are effective in the management of PHN. The combined NNT for TCAs is 2.64. The mechanism of action is thought to be by the inhibition of re-uptake of 5-hydroxytryptamine and norepinephrine which modulates descending pain pathways. TCAs are associated with significant side-effects such as orthostatic hypotension, sedation, urinary retention, memory loss, dry mouth, constipation, and cardiac conduction abnormalities. NNH for minor side-effects was 5.67 and for major side-effects 16.9. Serotonin and norepinephrine reuptake inhibitors (SNRIs: venlafaxine and duloxetine) are a newer class of drugs with proven efficacy in neuropathic pain though the evidence in PHN is lacking.

Opioids

Data from single RCTs have shown that oxycodone, morphine, and methadone significantly reduce the pain of PHN. In a cross-over RCT, morphine and methadone were found to be as effective as the TCAs nortriptyline and desipramine. The combined NNT for opioids in PHN is 2.67. Opioids exert their analgesic effects by acting on opioid receptors involved with pain modulation. Side-effects include sedation, constipation, pruritus, nausea and vomiting, and orthostatic hypotension. Data from one RCT showed that oxycodone has an NNH for minor side-effects of 3.57 and for major harm 50. Side-effects may be most problematic during initiation of therapy and as dosage increases but decrease in intensity as the patient becomes tolerant. However, the use of opioids for chronic non-cancer pain remains somewhat controversial.

A single placebo controlled RCT has demonstrated the efficacy of orally administered controlled release tramadol with an NNT of 4.76. Tramadol has a dual mechanism of action by activating μ-opioid receptors and also by decreasing reuptake of norepinephrine and serotonin. The most commonly reported adverse events associated with tramadol resemble those of opioids: constipation, nausea, dizziness, somnolence, and vomiting. Some patients may experience orthostatic hypotension, which may be difficult for an elderly patient to tolerate. Tramadol may be problematic in a patient with a known seizure history or epilepsy or if administered concomitantly with medications that lower an individual’s seizure threshold or those at risk of serotonin syndrome (those taking selective serotonin reuptake inhibitors, SNRIs, or monoamine oxidase inhibitors).

Data on the efficacy of the combination therapy with opioids and other antineuropathic agents are limited but may be potentially beneficial.

Topical therapies

Three placebo controlled trials have shown the efficacy of lidocaine 5% patches/plasters for the treatment of PHN. Lidocaine blocks abnormal sodium channel activity, and increased lidocaine binding to these channels would make it a potentially effective agent. However, lack of pain as a primary outcome and the difficulty of meta-analysis due to non-dichotomous data have led to certain authorities questioning the evidence base of the use of topical lidocaine for PHN. Nevertheless, the incidence of side-effects of topical lidocaine is extremely low, and lidocaine patches/plasters are frequently included in treatment guidelines. There is no evidence for the effectiveness of lidocaine gel on PHN.
Capsaicin is an agonist at the vanilloid receptor (the transient receptor potential channel TRPV1) which is present on the terminals of primary nociceptive afferents. On initial application, it has an excitatory action and produces burning pain and hyperalgesia. Capsaicin is thought to reduce pain by depleting substance P from sensory nerve endings and by causing a reversible loss of epidermal nerve fibres. Topical capsaicin 0.075% reduces pain in PHN with an NNT of 3.26. Patients should apply the formulation to intact skin at the affected area four times daily, avoiding contact with mucous membranes, and ideally wear gloves for application. Side-effects include burning, stinging, and erythema on application. The NNH for minor side-effects has been reported as 3.94 and 4.67 for major harm (from a single RCT). This high attrition rate is unsurprising since the area of patch placement may be hyperalgesic and allodynic. Tolerability and therefore compliance may be improved by prior application of local anaesthetic cream. Recent RCTs have shown the efficacy of single application of 8% capsaicin patch for long-term benefit in PHN.

Evidence for the use of other topical treatments such as non-steroidal anti-inflammatory medicines is limited, although one RCT for topical aspirin and diethyl ether showed benefit.

Other pharmacological treatments

N-Methyl-D-aspartate receptor antagonists (dextromethorphan and memantine) have also been trialled but did not show any superiority over placebo and their use remains limited.

### Interventions

A number of interventional strategies including local anaesthetic infiltration, peripheral nerve blocks, dorsal root ganglion blocks, sympathetic nerve blocks, epidural local anaesthetic injection with or without steroids, and intrathecal steroids have been tried in the prevention and treatment of PHN, but the evidence is limited.

Two studies have demonstrated the efficacy of intrathecal administration of methylprednisolone and lidocaine in patients with PHN. One proposed mechanism is by the steroid-induced reduction in inflammatory mediators (such as interleukin-8) which are raised in cerebrospinal fluid (CSF) of patients with intractable PHN. Although these studies reported few side-effects, this technique is not widely used probably because of the practical issues of repeated intrathecal injections.

Sympathetic nerve blocks are used both for acute pain associated with herpes zoster and chronic pain of PHN. They include stellate ganglion block for craniofacial involvement and thoracolumbar sympathetic blocks for truncal involvement. The evidence suggests efficacy only for short-term pain control and limited long-term efficacy.

Transcutaneous electrical nerve stimulation may be effective in some cases with few side-effects. Analgesia is reportedly due to an increase in levels of endorphin and enkephalin in response to low-level electrical stimulation. It may be especially useful in patients with associated myofascial pain.

Spinal cord stimulation is recognized as an important modality in the management of chronic neuropathic pain. However, there are no RCTs for its use in PHN.

### Medications used

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Titration</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Start at 100–300 mg daily</td>
<td>Increase gradually every 5 days to a maximum of 1800 mg/day</td>
<td>Somnolence, dizziness, fatigue, ataxia</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>75 mg twice daily (start at 25 mg in frail patients)</td>
<td>Increase to 150 mg twice daily within 1 week</td>
<td>Somnolence, dizziness</td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline, nortriptyline</td>
<td>10–25 mg at night</td>
<td>Increase by 10–25 mg every 7 days to a maximum of 100 mg nightly</td>
<td>Sedation, xerostomia, confusion, dysrhythmias, weight gain, dizziness</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Start at 5–10 mg every 4–6 hourly</td>
<td>Titrated as needed for pain and change to 12 hourly sustained release</td>
<td>Nausea, constipation, sedation, hormonal changes</td>
</tr>
<tr>
<td>Morphine immediate release</td>
<td>Start at a dose of 5–10 mg every 4 hourly as needed</td>
<td>Titrated to sustained release 12 hourly preparation</td>
<td>Nausea, constipation, sedation, hormonal changes</td>
</tr>
<tr>
<td>Methadone</td>
<td>2.5–5 mg three times daily</td>
<td>Titrated as needed for pain, though titration may be difficult</td>
<td>Nausea, constipation, sedation, hormonal changes</td>
</tr>
<tr>
<td><strong>Other classes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>50–100 mg four times a day</td>
<td></td>
<td>Nausea, emesis, dizziness, vertigo, somnolence, headache, constipation</td>
</tr>
<tr>
<td><strong>Topical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% Lidocaine transdermal</td>
<td>One patch daily for a maximum of 12 h per 24 h</td>
<td>Can be increased to three patches a day</td>
<td>Local skin irritation</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>0.075% (cream/loction) on intact skin up to 4 times a day</td>
<td>None</td>
<td>Localized burning sensation and skin irritation</td>
</tr>
</tbody>
</table>

Post-herpetic neuralgia
Treatment guidelines

Childhood vaccination will help in reducing seropositive individuals in the population. Prompt treatment of acute zoster with antiviral medication decreases pain and the likelihood of developing PHN especially those with ophthalmic involvement and in patients more than 50 yr old.

TCAs (e.g. amitriptyline and nortriptyline) and gabapentinoids (gabapentin and pregabalin) have been found to be effective treatments for PHN. Nortriptyline potentially has a better side-effect profile and should be preferred over amitriptyline especially in the elderly. Gabapentin or pregabalin are also considered first line and may be given alone or in conjunction with other analgesics. Opioids may be added to patients not responding to the above agents especially with severe pain. Lidocaine patches have been found effective for the treatment of PHN and should be considered with or without the other first-line treatments. Topical capsaicin, if tolerated, also has analgesic potential and the 8% capsaicin patch offers a novel treatment. Other medications or interventions for which there is some but limited efficacy data are possible options for refractory pain if first-line treatments are ineffective.

Declaration of interest

P.F.S., in the last 3 years, has served as consultant to Prostrakan, Napp, Grunenthal, Meda UK, Archimedes and Nycomed. He has also received payment for lectures from Pfizer.

References


Please see multiple choice questions 9–12.