

# Postherpetic neuralgia in everyday practice

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## Abstract

Postherpetic neuralgia is a complication following 10% of herpes zoster infections. It is a complex pain syndrome, thought to be driven by peripheral factors and central nervous system sensitisation. Herpes zoster is common in South Africa. It is important to identify high-risk patients and intervene early to reduce the likelihood and severity of postherpetic neuralgia (PHN). This review discusses a stepwise approach to the treatment of PHN in primary care.

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## Introduction

Postherpetic neuralgia (PHN), a chronic pain syndrome, is often diagnosed when pain persists in a dermatomal pattern four to six weeks after the herpes zoster vesicular eruption has healed.<sup>1</sup>

PHN follows as a complication of shingles in 10-15% of patients, and can last for months to years.<sup>2</sup> Generally, the pain improves over time, and overall, around 3% of patients with herpes zoster have pain that persists for more than three months, while only 2-5% have pain that lasts longer than a year.<sup>3</sup> Some studies have suggested a much higher incidence of PHN, quoting 50-60% of people who experience pain one month post-varicella zoster infection, which then decreases with time.<sup>4</sup>

## Postherpetic neuralgia in perspective

South Africa is particularly affected by herpes zoster and the complications thereof, because of the overall prevalence of human immunodeficiency virus (HIV) infection. A person's lifetime risk of herpes zoster infection is 15-20%, with the highest incidence occurring in the elderly and immunocompromised. HIV infection is associated with a 10-fold increase in the risk of herpes zoster infection, and this risk remains increased, even when taking highly active antiretroviral treatment.<sup>5</sup> While no studies have specifically investigated the incidence of herpes zoster and PHN in South Africa, the widespread HIV epidemic makes this condition and its complications a real concern for South African healthcare practitioners.

## Mechanism of postherpetic neuralgia

Different pathophysiological mechanisms, sensitisation and deafferentation, can explain the pain of PHN:<sup>6</sup>

- *Peripheral sensitisation*: Subsequent to tissue injury, nociceptors become sensitised, resulting in spontaneous discharge activity and hyperexcitability.<sup>6</sup>
- *Central sensitisation*: The exaggeration of dorsal horn neuron response to afferent stimuli, and the expansion of receptive fields by prolonged nociceptor discharge, may lead to allodynia without sensory loss.<sup>6</sup>
- *Deafferentation pain*: Reactivation of the varicella zoster virus results in neural damage and inflammation, with subsequent oedema.<sup>6</sup>

Other mechanisms for PHN pain include neuroma formation or neuronal sprouting, and local axons reinnervating previously denervated areas.<sup>7</sup>

## Predicting risk

The risk of developing PHN increases depending on certain factors, including:

- *Increasing age*: Approximately 80-85% of PHN develops in herpes zoster patients who are more than 50 years old.<sup>8</sup>
- *Severe prodromal dermatomal pain*, before the onset of the rash.<sup>9</sup>
- *Severe pain*, and the *extent of the rash*.<sup>9</sup>
- *Site of the herpes zoster*: The jaw, neck and sacral and lumbar areas affected by herpes zoster are low-risk sites, while the thoracic area is a moderate-risk site. The highest-risk sites are the trigeminal nerve (especially the ophthalmic division) and the brachial plexus.<sup>10</sup>

## Clinical presentation

The pain of PHN can persist for weeks, months, and on occasion, years. The pain has been described as mild to excruciating in severity; and from constant, intermittent,

and lasting for a few minutes, to being constant daily, or almost daily.<sup>11</sup>

The pain can be constant, deep, or burning, and can include intermittent sharp, stabbing, or shooting sensations. These patients may also have allodynia, and may be unable to wear clothing that covers the allodynia area. Dressing, bathing, grooming and mobility may be effected.<sup>12</sup>

The severity of the pain of PHN can have a significant negative impact on a person's quality of life, and can be very debilitating. PHN patients can experience chronic fatigue, anorexia, weight loss and depression.<sup>11</sup> Their social role may change from being active in the community, to inactive. Some people rarely leave their homes.<sup>13</sup> PHN has been stated to be one of the most common causes of pain-related suicide in the elderly.<sup>13</sup>

### Prevention and treatment

While there is no method to entirely prevent PHN, early use of antiviral therapy in high-risk individuals, aggressive pain control, and population-based vaccination are all useful strategies.

Ongoing treatment options include antidepressants, anticonvulsants, topical treatments, and continued use of analgesics. Forty per cent of PHN pain is resistant to all treatment, highlighting the need for timely antiviral therapy in herpes zoster.<sup>14</sup>

The stepwise approach to treatment of PHN is summarised in Table I.

#### Antiviral agents

Use of an antiviral agent within 72 hours of the rash appearing has been shown to reduce the overall duration of pain associated with PHN.<sup>16</sup>

The antiviral agents, acyclovir, valacyclovir, and famcyclovir, are highly selective for thymidine kinase, an enzyme encoded by the herpes zoster virus, and ultimately inhibit viral replication. They reduce the duration of viral shedding and lesion formation, which speeds up recovery and reduces the risk of PHN.<sup>17</sup>

While valacyclovir and famcyclovir have similar effectiveness in the resolution of PHN pain, they have been found to be more effective than acyclovir at six months.<sup>18,19</sup>

Antiviral agents are recommended within 72 hours of the development of herpes zoster symptoms in patients:

- Over 50 years old<sup>20</sup>
- With high-risk areas affected by PHN<sup>21</sup>
- With moderate-to-severe pain, or a rash
- Who are immunocompromised.<sup>22,23</sup>

#### Corticosteroids

Studies have demonstrated that steroids may offer some pain relief during the acute phase of herpes zoster infection, but do not reduce the likelihood or severity of PHN.<sup>3</sup>

#### Herpes zoster vaccine

A live attenuated varicella vaccine (Zostavax®) is available in the USA, Australia and Europe. It is not yet available in South Africa. Zostavax® has shown a significant reduction (51%) in the development of herpes zoster, and PHN (61%), in people over the age of 60 years.<sup>15</sup>

#### Antidepressants

##### Tricyclic antidepressants

Tricyclic antidepressants, such as desipramine and amitriptyline, are recommended as first-line agents in the treatment of PHN. In addition to their effect of alleviating depression, these agents also have analgesic properties.

**Table I: Stepwise approach to treating postherpetic neuralgia<sup>15</sup>**

Step	Therapy	Comments
1	Non-opioid (simple analgesics) ± weak opioids: <ul style="list-style-type: none"> <li>• Paracetamol</li> <li>• Paracetamol and codeine 30 mg (treat constipation prophylactically)</li> <li>• Tramadol</li> </ul>	Use non-opioids first. Consider adding opioid analgesics, if pain is unresponsive. Test tolerance to tramadol with an initial trial of 50 mg oral, then switch to slow-release 100-200 mg oral twice daily. Use lower doses in older people. While nonsteroidal anti-inflammatory drugs may be useful in managing acute zoster pain, there is no evidence to support their use in postherpetic neuralgia.
2	Tricyclic antidepressant or antiepileptic drugs Above options, and/or <ul style="list-style-type: none"> <li>• Nortriptyline or amitriptyline, initially, 10 mg orally at night, or</li> <li>• Pregabalin, initially 75 mg oral at night</li> </ul>	Increase tricyclic antidepressant dose by 10 mg every 2-3 days, as tolerated, to a maximum of 75 mg/day. Conduct a trial at this dose for three weeks to assess efficacy. Use a lower dose at night, or for older people (maximum of 25-50 mg/day). Increase pregabalin by 75 mg every 2-3 days, as tolerated, to 300 mg twice daily. Conduct a trial at this dose for two weeks to assess efficacy.
3	Strong opioids Above options, and/or morphine	Test tolerance with an initial small-dose trial, then switch to morphine 10 mg twice daily. The maximum dose should rarely exceed 60 mg/day. Use lower doses in older people.
4	Alternative therapies: <ul style="list-style-type: none"> <li>• Imipramine, desipramine</li> <li>• Gabapentin</li> <li>• Topical capsaicin</li> <li>• Topical lignocaine</li> </ul>	Trial alternative tricyclic antidepressants and anti-epileptic drugs. Consider other adjuvant therapies listed. A topical lignocaine patch is effective if allodynia is present, but it is currently unavailable in South Africa.

This is most likely because of their action of blocking the reuptake of monoamine neurotransmitters released by descending axons from the brainstem.<sup>3</sup>

In one randomised control trial, patients (> 60 years of age), initiated with amitriptyline within 48 hours of the onset of herpes zoster symptoms, showed a 50% decrease in pain prevalence at six months compared to placebo.<sup>24</sup> Desipramine and nortriptyline, both of which have a predominant norepinephrine reuptake blocking action, appear to be as effective as amitriptyline in PHN.<sup>25</sup> Patients respond to desipramine and nortriptyline at doses comparable to those of amitriptyline, but with fewer anticholinergic side-effects and significantly less sedation.<sup>26</sup>

### Other antidepressants

Overall, while alternative antidepressants have fewer side-effects than tricyclic antidepressants there is little supporting evidence around their use in PHN. Venlafaxine and duloxetine are recommended as alternative agents where tricyclic antidepressants are contraindicated, or poorly tolerated. They block both serotonin and norepinephrine reuptake, and have demonstrated efficacy in painful diabetic neuropathy.<sup>27,28</sup>

Selective serotonin reuptake inhibitors are an alternative class, and both fluoxetine and paroxetine have been found to be useful in some patients.<sup>21</sup> As yet, there are no controlled clinical trials on these agents in PHN, and they are regarded as a second-line treatment only.<sup>26</sup>

### Antiepileptics

Gabapentin and pregabalin have both been shown to offer proven benefit in the treatment of PHN pain. While they both reduce pain and improve sleep and quality of life, they are associated with unpleasant side-effects such as somnolence, dizziness, ataxia, and peripheral oedema, which do limit usage.<sup>29,30</sup>

Pregabalin and gabapentin bind to the  $\alpha_2\delta_1$  subunit subunit of voltage-gated calcium channels, decreasing calcium influx and inhibiting the release of excitatory neurotransmitters.<sup>31</sup> Pregabalin has a greater binding affinity than gabapentin,<sup>32</sup> and has been found to reduce the need for additional analgesia more so than gabapentin, following retrospective review. Pregabalin is recommended in preference to gabapentin, where the option is available.<sup>33</sup>

Carbamazepine and oxcarbazepine are very effective in treating trigeminal neuralgia. However, there are no controlled studies in PHN.<sup>25</sup> Newer anticonvulsants, such as lamotrigine, also have some utility in the treatment of peripheral and central neuropathic pain. However, there is insufficient evidence to support their use in PHN.<sup>26</sup>

### Analgesics

#### Topical therapy

- Lidocaine: Topical 5% lidocaine patches have been demonstrated as effective in relieving pain and allodynia in patients with PHN.<sup>34</sup> There is limited systemic

uptake, and side-effects are minimal. In South Africa, 5% lidocaine patches are only available in doses of 25 mg. The recommended dosage for managing PHN is a patch containing 700 mg of lidocaine.<sup>35</sup> Topical local anaesthetic creams and gels are available in South Africa, and applied below an occlusive dressing, may provide some pain relief.<sup>3</sup>

- Capsaicin: Capsaicin is a chili derivative, which has been found to be of some value in PHN. Capsaicin works by stimulating, and then inhibiting, nociceptive C nerve fibres.<sup>21</sup> The initial stimulation can be painful, causing intense burning, and up to one third of patients are unable to tolerate the treatment.<sup>36</sup>

### Systemic treatment

#### Opioid analgesics

Although only a few controlled studies are available that have assessed the effect of acute pain therapy on the development of PHN, all modern concepts of pain generation suggest that every acute pain input to the nervous system will lead to chronification.<sup>37,14</sup>

While neuropathic pain is typically less responsive to traditional analgesics, slow-release opioids and morphine sulphate are recommended by the American Academy of Neurology as first-line agents in the treatment of PHN.<sup>38</sup>

Paracetamol alone, and in combination with mild opioids, should always be used before recommending stronger opioids.<sup>14</sup> Nonsteroidal anti-inflammatories have no proven use in the treatment of PHN, and may cause significant side-effects.<sup>14</sup>

Opioids do raise concerns around side-effects, tolerance and addiction, but studies continue to demonstrate their effectiveness when used appropriately to treat PHN.<sup>39-42</sup>

Opioid analgesic therapy causes side-effects, including constipation, sedation and nausea. Concomitant use of fibre-containing laxatives should be recommended to all opioid users.<sup>14</sup> Opioid analgesics should be used cautiously in patients with a history of substance abuse.<sup>17</sup>

#### Interventional strategies

Interventional treatment options for PHN include sympathetic blocks, epidural and intrathecal methylprednisolone, and spinal cord stimulators.<sup>26</sup> There is limited evidence of effectiveness, as well as a high risk of complications in these procedures.<sup>38</sup> They are reserved in those patients where other pain interventions have failed. A pain specialist would need to manage interventional pain procedures.

### Referral

Patients should be referred to a pain specialist for further management if:

- Advice and initial treatment fail to control pain within four to six weeks.

- Adverse effects, or special circumstances, limit treatment options.
- Second- or third-line treatments, such as carbamazepine, strong opioids or interventional strategies, are being considered.<sup>21</sup>

## Conclusion

PHN is a complication of herpes zoster, and is a common and debilitating condition. While no treatment entirely prevents PHN, early use of antiviral agents, effective analgesia, tricyclic antidepressants, and pregabalin can help to reduce the severity and length of PHN following herpes zoster.

PHN appears to involve several possible mechanisms. The concomitant use of two or more analgesics, preferably with an atypical agent, with different mechanisms of action provides greater pain relief than a single agent. The advantages of using drug combinations must be weighed against complications resulting from drug interactions which can be life-threatening, e.g. tramadol with tricyclic antidepressants.

The South African HIV epidemic fuels the prevalence of herpes zoster, and the complications thereof. Early effective identification and intervention of herpes zoster and PHN are necessary to prevent chronic ongoing and debilitating pain.

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