

# Post-herpetic neuralgia

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**Background:** In spite of the large body of evidence available in the literature, definition and treatment of Post-Herpetic Neuralgia (PHN) are still lacking a consistent and universally recognized standardization. Furthermore, many issues concerning diagnosis, prediction and prevention of PHN need to be clarified in view of recent contributions.

**Objectives:** To assess whether PHN may be better defined, predicted, treated and prevented in light of recent data, and whether available alternative or adjunctive therapies may improve pain relief in treatment recalcitrant PHN.

**Methods:** Systematic reviews, meta-analyses, randomized controlled trials, cohort studies and protocols were searched; the search sources included PubMed, Cochrane Library, NICE, and DARE. More than 130 papers were selected and evaluated.

**Results:** Diagnosis of PHN is essentially clinical, but it can be improved by resorting to the many tools available, including some practical and accessible questionnaires. Prediction of PHN can be now much more accurate, taking into consideration a few well validated clinical and anamnestic variables. Treatment of PHN is presently based on a well characterized array of drugs and drug associations, including, among others, tricyclic antidepressants, gabapentins, opioids and many topical formulations. It is still unsatisfactory, however, in a substantial proportion of patients, especially those with many comorbidities and intense pain at herpes zoster (HZ) presentation, so that this frequent complication of HZ still strongly impacts on the quality of life of affected patients.

**Conclusion:** Further efforts are needed to improve the management of PHN. Potentially relevant interventions may include early antiviral therapy of acute HZ, prevention of HZ by adult vaccination, as well as new therapeutic approaches for patients experiencing PHN.

**Keywords:** pain relief, PHN treatment, PHN predictors, PHN prevention

## Introduction

### Definition and clinical presentation

Herpes zoster (HZ) is a self-limiting disease, with pain quenching at the end of vesicular eruption. In a significant proportion of patients, however, pain can persist or relapse months to years after rash healing, being then referred to as post-herpetic neuralgia (PHN). Pain in PHN is described as burning, throbbing, lancinating, or electric-shock-like, and intermittent or continuous. PHN is sometimes associated with allodynia or hyperesthesia, spreading at the same dermatome(s) as in HZ.

The definition of PHN has been a matter of discussion for a long time, being defined at different time intervals after rash healing in HZ. PHN has been defined as pain persisting or resuming 4, 6, 8, 12 weeks, or even 6 months after rash healing.<sup>1-12</sup>

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At the end of the 1990s, Dworkin and Portenoy<sup>1</sup> proposed a definition that was widely accepted: they set the diagnosis of PHN at 3 months after rash healing, referring to pain persisting at earlier time points as zoster-associated pain (ZAP). More recently, this definition has been revised, with a further distinction:<sup>2,3,6</sup> pain present within 30 days from the onset of rash is defined as acute herpetic neuralgia; pain present between 30 and 120 days is defined as subacute herpetic neuralgia; pain persisting after 120 days from the onset of HZ is defined as PHN. Moreover, other authors introduced the concept that only clinically relevant pain should be defined as PHN, to avoid overestimation of the problem: they proposed PHN to be defined as pain  $\geq 3$  on a 10-point scale persisting 120 days after rash healing.<sup>4,5,7</sup>

Different tools have been assessed to quantify and qualify pain in PHN. Verbal rating scales are easy to handle in real clinical settings, but have limited value to stratify and characterize pain. Visual analog scales (VASs) have been extensively investigated and used in various settings of pain clinical management,<sup>4,13</sup> allowing a more precise identification of the single patient's pain level, and being easily understood by patients. Furthermore, PHN has been considered in recent years as a continuum rather than a partition of herpetic pain and total pain burden measured with a single comprehensive parameter by Coplan et al,<sup>5</sup> who used an area-under-the-curve (AUC) method to combine measures of HZ pain intensity and duration. AUC highly correlated with other pain, quality of life, and activities of daily living validated questionnaires.<sup>7</sup>

The AUC method was similarly adopted by other authors with subtle variations.<sup>12,14</sup> A recent Italian prospective study used verbal rating pain scores instead of worst pain scores.<sup>12</sup> Drolet et al<sup>14</sup> considered only pain relevantly affecting quality of life and activities of daily living, that is pain scored  $\geq 3$  on a 0–10 scale. All these attempts ushered a potentially relevant tool to better estimate the impact of HZ and PHN in real life, and to thoroughly assess the cost-efficacy of vaccination for HZ.

Diagnosis of PHN is essentially clinical. VAS and the McGill Pain Questionnaire, as structured diagnostic tools, are useful and validated to quantify and qualify the patient reported pain. Thorough investigation of other possible underlining causes of neuralgia (eg, neoplastic, toxic, traumatic, and compressive) should be carried out when appropriate. Further structured tools have been developed in recent years: the McGill Pain Questionnaire in its short form<sup>15</sup> was widely used for pain evaluation in a consistent fraction of more recent studies.<sup>4,16,17</sup> Zoster Brief Pain Inventory

(ZBPI) is the more specific tool designed specifically for HZ pain:<sup>5</sup> it includes discomfort other than pain, such as itching, occurring in the same area as HZ rash. It measures the severity of pain (current, least, and worst) in the last 24 hours on a 0–10 scale, together with HZ pain interference with various activities of daily life. This tool was shown to have good validity in the context of ZAP and PHN.<sup>5,7</sup> The lack of a consistent definition of PHN, however, may still hamper a proper management of PHN. In view of the recent literature, proper definition of PHN should refer to relapsing or long-lasting herpetic pain at least 3 months after HZ. Quantification of patient-reported pain, furthermore, may be ill-defined without appropriate tools.

## Etiology

The understanding of the pathophysiological mechanisms underlying the onset of chronic pain in PHN is still an open challenge. The initial viral replication causes direct damage by neuritic inflammation on the rear dorsal root, resulting in necrosis, fibrosis, and destruction of nerve tissue from peripheral afferent fibers to the spinal cord.<sup>18,19</sup> Several studies have documented atrophy of the posterior horn in the spinal cord, fibrosis of the posterior root ganglia, and loss of cutaneous innervation, with pathological degeneration of cell bodies and axons of primary afferent neurons,<sup>20</sup> determining hypoesthesia and paresthesia in association with pain. However, the precise mechanism(s) at the basis of pain in PHN remain unclear, and attempts to draw a single unifying theory are inconclusive. The pathophysiology of PHN may involve both peripheral and central mechanisms, such as gate control, viewing PHN as a chronic pain syndrome due to deafferentation,<sup>21</sup> or strengthening of existing synaptic connections between central pain pathways and peripheral A $\beta$  fibers.<sup>22</sup> However, several studies have revealed interesting aspects about central nervous system (CNS) support cells and structures, evaluating the role of the immune system in the pathogenesis of PHN, as glia cells (astrocytes and oligodendrocytes) and their receptors produce factors influencing neuronal functioning.<sup>23,24</sup> Damage of myelinated fibers would activate Schwann cells and satellite cells, in turn releasing neuro-excitatory mediators such as tumor necrosis factor- $\alpha$ .<sup>25,26</sup> Other support structures putatively involved in the pathogenesis of chronic pain are vasa nervorum and nervi nervorum.<sup>27–29</sup> The hypothesis that the activation of trophic and support structures of peripheral nerves would play an important pathogenic role in PHN may have important therapeutic implications.<sup>19</sup> Another hypothesis by Gilden et al<sup>30</sup> suggests the potential role of persistent varicella-zoster virus (VZV) replication and chronic

ganglionitis resulting in PHN. A Chinese work published in 2009 analyzed the relationship between pro-inflammatory cytokines in acute HZ and the development of PHN, showing that patients with PHN had higher interleukin-6 serum levels.<sup>28,31</sup> The role of calcitonin gene-related peptide (CGRP) in triggering chronic pain conditions has also been recently explored.<sup>32</sup> The differential expression and regulation of CGRP isoforms may be a detectable signal involved in sensory transduction and modulation, as well as in contributing to chronic pain mechanisms.<sup>32</sup>

The different hypotheses so far postulated are not mutually exclusive, and the pathophysiology of chronic pain in PHN may well be multifactorial. Therefore, further studies are needed to allow a more comprehensive view of this severe and disrupting condition and to develop targeted therapies for PHN.

## Economics

Until 2006, few published studies addressed the economic burden of PHN directly (in general together with HZ or diabetic neuropathy), mostly including costs of medications, outpatient visits, hospitalization and length of stay, and loss of working days. Mean costs for estimated PHN episodes per year in Italy were as high as EUR 33.7 million.<sup>33</sup>

## Methods

Systematic reviews, meta-analyses, randomized controlled trials (RCTs), cohort studies and protocols were searched and the search sources include PubMed, Cochrane Library, NICE, and DARE. Articles were searched using the following key words: “post herpetic neuralgia”, “post herpetic neuralgia treatment”, “post herpetic neuralgia predictors”, “post herpetic neuralgia etiology”, “neuropathic pain”, “neuropathic pain assessment”, wherever occurring in the text. Among the many papers retrieved, approximately 120 were selected and quoted.

## Results

### Prediction of PHN

No systematic reviews, meta-analyses, or RCTs had evidence pertaining to the prediction of PHN. However, 14 cohort studies did.<sup>6,8–12,34–41</sup>

Predictors of PHN in the acute phase of HZ have been extensively investigated in order to point out patients who are at higher risk of developing this painful syndrome and need to be monitored more carefully during follow-up.

Older age is one factor associated with PHN in almost all studies, whenever investigated.<sup>6,8–12,34–38</sup> Central and

peripheral nervous systems in the elderly may less efficiently tolerate the damage associated with VZV reactivation and the consequent burst of immune response (see Table 1).<sup>42</sup>

Pain at presentation is the second best-established risk factor for PHN (see Table 1). Trials on antiviral therapy for HZ suggested the importance of pain intensity at presentation in predicting PHN;<sup>35,39</sup> several cohort studies have confirmed these data in real life<sup>6,9–12,36,38,40</sup> (see Table 1). The pathogenesis of this correlation is still unclear: the intensity of acute pain may reflect central structural and functional processes, such as excitotoxic damage in the dorsal horn, and damage to primary afferent nociceptors.<sup>43</sup>

Severity of rash, assessed as the number of lesions appearing on the patients' skin at presentation, suggests a relationship between the extent of neural damage and PHN (see Table 1).<sup>6,10,35,37–39,41</sup>

The presence and duration of symptoms prodromal to HZ rash (pain, dysesthesia, and allodynia) have been reported as tightly predictive of PHN in several studies.<sup>6,36,40,44</sup> This association may reflect a more intense involvement of nerve fibers by viral reactivation in the early phases of HZ, leading to extended damage and PHN.<sup>45</sup>

In a few reports, PHN has been reported as more frequent in ophthalmic and thoracic zoster patients,<sup>10</sup> suggesting a predictive role of HZ localization. Higher levels of VZV DNA at HZ presentation were also suggested as an independent predictor of pain persistence.<sup>9</sup> Surgical interventions and mechanical trauma were associated with a higher risk of HZ, but their possible role in predicting PHN has been poorly investigated. In a recent prospective survey on 519 HZ patients,<sup>12</sup> trauma was associated with a higher risk of PHN (see Table 1). Furthermore, cigarette smoking has been scantily evaluated as a possible risk factor for pain intensity at presentation of PHN. In the same survey,<sup>12</sup> smoke was associated with both higher pain at presentation and higher risk of PHN.

Psychosocial factors have been proposed to be associated both with a higher ZAP burden and higher risk of PHN. Depression, together with the severity of HZ disease at presentation, was associated with higher pain intensity and ZAP burden.<sup>44</sup> In a small prospective study,<sup>46</sup> greater anxiety, greater depression, lower life satisfaction, and greater disease conviction were predictors at baseline for chronic zoster pain. Hence, psychological factors may be useful in evaluating patients with HZ.

Finally, female sex has been proposed as a predictor of PHN, not yet reaching, however, a convincing level of evidence so far.<sup>6,10,12</sup>

Table 1 Predictors of PHN in trials and cohort studies quoted to this purpose

Study	Patients	Study design	PHN definition	Older age	Female sex	Greater acute pain severity	Greater rash severity	No antiviral therapy for HZ	Presence of a prodrome	HZO Deposition	Duration of prodrome	VZV viremia at presentation	Others
Choo et al <sup>34</sup>	821 HZ – PHN nd	Retrospective	Pain persisting 1 and 2 months after rash onset	X					X				
Dworkin et al <sup>35</sup>	419 HZ – 129 (nd) PHN	Famciclovir trial	Pain following rash healing, 1 (and 3) months after HZ diagnosis	X		X	X <sup>c</sup>						
Whitley et al <sup>39</sup>	nd	Acyclovir and prednisone trial	Time to cessation of acute neuritis and ZAP (Cox)			X							
Decroix et al <sup>36</sup>	1897 HZ – PHN nd	Open-label valacyclovir study	Time to cessation of ZAP (Cox)	X		X		X	X				
Opstelten et al <sup>8</sup>	837 HZ – 54 PHN	Retrospective	Pain 1 month after HZ diagnosis	X						X			
Nagasako et al <sup>41</sup>	1778 HZ – PHN nd	Four famciclovir trials	Pain present 3 months after rash onset			X							
Kurokawa et al <sup>37</sup>	263 HZ – PHN nd	Prospective	Pain persisting 3–6 months after HZ diagnosis	X		X							Disturbed sleep, hypanesthesia
Scott et al <sup>9</sup>	278 HZ – 42 (78) PHN	Prospective	Pain present at 6 weeks (and 3 months) after HZ diagnosis	X		X						X	
Jung et al <sup>6</sup>	965 HZ – 114 PHN	Two famciclovir trials	Pain persisting 120 days after rash onset	X		X			X				
Katz et al <sup>40</sup>	129 HZ – 20 PHN	Prospective	Pain 120 days after rash onset			X			X	X			
Opstelten et al <sup>38</sup>	598 HZ – 46 PHN	Prospective (in the PINE study)	Pain $\geq$ 30 VAS 3 months after HZ diagnosis	X		X							Trust in health care
Volpi et al <sup>10</sup>	219 HZ – 70 PHN	Prospective	Pain present 6 months after HZ diagnosis	X		X			X		X		
Parruti et al <sup>12</sup>	519 HZ – 226 (130) PHN	Prospective	Pain persisting/relapsing 1 (and 3) months after HZ diagnosis	X		X							Trauma, smoke
Drolet et al <sup>11</sup>	249 HZ – 56 PHN	Prospective	Pain $\geq$ 3/10 VAS persisting 3 months after HZ diagnosis	X		X							Limited functional status

**Notes:** <sup>a</sup>Patients receiving antiviral therapy (famciclovir versus placebo) had a significantly lower prevalence of PHN; <sup>b</sup>there was a higher percentage of patients developing PHN among those who did not receive (any) antiviral therapy. **Abbreviations:** HZ, herpes zoster; HZO, herpes zoster ophthalmic; nd, not declared; PHN, post-herpetic neuralgia; PINE, Prevention by Epidural Injection of Postherpetic Neuralgia in the Elderly; VAS, visual analog scale; VZV, varicella-zoster virus; ZAP, zoster-associated pain.

## Prevention of PHN

Five systematic reviews,<sup>47–51</sup> three RCTs<sup>7,35,52</sup> and one cohort study<sup>12</sup> contained evidence pertaining to the prevention of PHN; no meta-analyses did.

A potential role in prevention has been proposed for antivirals, according to the hypothesis that interrupting viral replication in the acute phase of HZ may reduce damage to nerve fibers and subsequent onset of PHN. Their role in PHN prevention, however, is still controversial: a recent Cochrane review<sup>47</sup> raises some doubts about their efficacy. In spite of that, studies with different designs suggest different conclusions. Vander Straten et al<sup>48</sup> suggested that antivirals in the acute phase of HZ appear to be effective in reducing PHN severity and duration, but not its incidence. Dworkin et al<sup>35</sup> found that patients receiving antiviral therapy (famciclovir versus placebo) had a significantly lower prevalence of PHN in a cohort study of 419 HZ patients. Parruti et al<sup>12</sup> showed that HZ patients not prescribed antivirals in the acute phase have a significantly higher risk of developing PHN, in a prospective cohort of 519 HZ unselected patients in a real-life clinical setting (see Table 1).

Corticosteroids prescribed in the acute phase of HZ have been shown to be ineffective in preventing PHN onset in several trials and in a recent review,<sup>49</sup> as well as antidepressants.<sup>50</sup> As greater acute pain severity predisposes to higher risk of PHN onset, pain relief in acute HZ has been investigated as to its possible preventive role. Interventional techniques, such as topical local anesthetics, subcutaneous local anesthetics and corticosteroids, percutaneous electrical nerve stimulation, and sympathetic and epidural blocks, have been proposed as prevention. They can produce an effective short-term pain relief in the acute phase, thus reducing the pain burden in this time frame, but their effect in reducing PHN remains unclear.<sup>51</sup>

The latest hypothesis investigated in the field of preventive pain relief in acute HZ is the combination of antivirals and gabapentin. In a recent study,<sup>52</sup> 133 consecutive patients with acute HZ were enrolled in a private dermatology clinic and treated with valacyclovir and gabapentin at currently recommended dosages, with a lower incidence of PHN at 6 months.

In 1995, vaccination for varicella with a wild-type VZV Oka strain was introduced under a Food and Drug Administration (FDA) recommendation, and at present, universal coverage vaccination programs are ongoing in the USA and several other countries. Varicella vaccine at higher dosage (at least 14 times) than in standard Varicella vaccination was demonstrated to be protective for the development of

HZ in the Shingles Prevention Study.<sup>7</sup> This was a randomized double-blind placebo-controlled trial including 38,546 healthy subjects aged over 60 years, randomly assigned to receive a mock vaccine or an investigational anti-VZV vaccine, and followed for 3.13 years on average after vaccination. The incidence of HZ was significantly reduced, from 11.1 per 1000 person-years in the placebo arm to 5.4 per 1000 person-years in the vaccine arm.<sup>7</sup> The incidence of PHN, defined as pain  $\geq 30/100$  at 90 days from the onset of rash, was similarly markedly reduced in the vaccine arm, from 1.38 to 0.46 per 1000 person-years. Moreover, vaccinated subjects developing HZ and PHN had significantly less pain and discomfort.<sup>5,7</sup> Therefore, zoster vaccination reduced overall HZ and PHN incidence by 51.3% and 66.5%, respectively in this large, pivotal study.<sup>7</sup>

Since HZ vaccine approval by the FDA for adults aged  $> 60$  in the United States in 2006, the real cost-effectiveness of HZ vaccination for the general population has been widely investigated. Several studies have assessed the economic burden of HZ and PHN, showing that they are frequent and costly conditions, also in terms of impact on quality of life.<sup>33,53–57</sup> In Italy, a recent study estimated that total annual costs for HZ and PHN were EUR 41.2 million, including both direct and indirect costs.<sup>33</sup> Vaccine cost-effectiveness was determined by decision models in multiple large countries (Canada, England and Wales, and USA), suggesting that immunization would increase quality-adjusted life-years.<sup>58–60</sup> In general, studies evaluating vaccine cost-effectiveness agree on its relevance in the elderly population.<sup>57,61–65</sup> It has been supposed that vaccination could be equally cost-effective in younger people aged  $< 50$ , as about 19% of HZ cases occur between 50 and 59 years of age. Further studies are ongoing to assess this point.

## Treatment of PHN

Nineteen systematic reviews,<sup>2,50,66–82</sup> 63 RCTs (mostly cited in the systematic reviews),<sup>2,50,66–82</sup> one longitudinal study<sup>83</sup> and one meta-analysis<sup>84</sup> showed evidence pertaining to this.

Pain relief in PHN with currently available therapies is often unsatisfactory. A large body of evidence (see Table 2) indicates that some pharmacologic agents, including opioids, tricyclic antidepressants (TCAs), antiepileptic drugs, and lidocaine patches, may result in at least partial pain relief for a limited proportion of patients with PHN, and that some of these patients may find the adverse effects of the above medications outweigh their benefits.<sup>66,67</sup> Fully effective treatment of PHN are still lacking, as its exact pathophysiological mechanisms are still elusive. Consequently, it is difficult to

establish specifically targeted therapies, a task calling for further research efforts. Indeed, as this condition does not adequately respond in many cases to any of the conventional agents tested, many efforts are ongoing even in the field of alternative therapeutic options. The management of PHN, however, is and will be complex, requiring a multidisciplinary approach, including drug therapy and nonpharmacological adjunctive therapies.

Several systematic reviews indicate that TCAs are effective in neuropathic pain and PHN,<sup>2,66,68</sup> being superior to selective serotonin reuptake inhibitors (SSRIs).<sup>50,69</sup> No studies so far have assessed the use of serotonin-noradrenalin reuptake inhibitors for this condition. It is believed that TCAs have an analgesic action by blocking the re-uptake of serotonin and norepinephrine, a blockade enhancing the inhibition of spinal cord neurons involved in pain perception.<sup>85</sup> Among TCAs, the most commonly used compounds are amitriptyline, nortriptyline, and desipramine.<sup>86,87</sup> Nortriptyline and desipramine are generally preferred to amitriptyline because they have recently been shown to be equally effective with a lower incidence of anticholinergic side effects such as sedation, orthostatic hypotension, cognitive decline, and constipation.<sup>66,70,87,88</sup> Other side effects include weight gain, blurred vision, and QT prolongation. Such side effects may be of particular concern in the elderly population and in patients with a history of cardiac arrhythmia or ischemic heart disease. Although there is no standard guidance for electrocardiogram (ECG) screening prior to their administration, TCAs may cause ECG changes (prolonged QT), and it may be prudent to obtain a baseline ECG in patients with cardiac disease.<sup>71,89,90</sup>

Among anticonvulsants, gabapentin and pregabalin have established efficacy in PHN, with several trials (see Table 2) showing the superiority of gabapentin versus nortriptyline.<sup>66,84,91,92</sup> Several RCTs and a few

meta-analyses have established the analgesic efficacy of gabapentin for the treatment of pain in PHN. RCTs have shown that a daily dose of 1800–3600 mg, given for 1–2 weeks, is effective in reducing pain and improving sleep, mood, and patient quality of life.<sup>18,72,93</sup> More recent studies have shown that a dose of 3600 mg daily can reduce pain by 43%.<sup>2</sup> The main reported side effects are drowsiness, dizziness, ataxia, mild peripheral edema, and a worsening of cognitive impairment in elderly patients. To reduce adverse events and increase compliance, gabapentin should be initially used at lower doses (100–300 mg in a single dose at bedtime) and then continued at a dose of 100–300 mg three times a day,<sup>73</sup> titrating the analgesic effect and the occurrence of side effects.<sup>18,71</sup> However, the efficacy of gabapentin in some patients with PHN may be limited by suboptimal drug exposure from unpredictable and saturable absorption. Recently, a new formulation of gabapentin (gabapentin enacarbil) has been developed for absorption by high-capacity transporters expressed throughout the intestine. It undergoes rapid post-absorption hydrolysis to gabapentin, providing sustained, dose-proportional drug exposure.<sup>94</sup>

Among gabapentinoids, both gabapentin and pregabalin are likely to provide analgesia by similar mechanisms of action. Although there are no meta-analyses examining the analgesic efficacy of pregabalin in PHN, there are a few RCTs in support. In 2004, the use of pregabalin for the treatment of diabetic neuropathy and PHN was approved in Europe and the United States. An RCT in 2004 showed the effectiveness of this drug in the treatment of PHN.<sup>95</sup> Pregabalin was well tolerated even by elderly patients. The commonly reported side effects were drowsiness, dizziness, and mild peripheral edema. The optimal dose to be administered has not yet been thoroughly assessed. Other recently studied antiepileptic drugs are sodium divalproate and oxcarbazepine, which

**Table 2** Available evidence to support the use of several drugs or drug classes in the treatment of PHN

Drug or drug class	Trials (N)	Participants	Comparator drug(s)	Outcome
Gabapentin <sup>2,18,66,71–73,84,91–93</sup>	16	2798	Placebo/nor-amitriptyline	+
Gabapentin enacarbil <sup>94</sup>	1	101	Placebo	+
Pregabalin <sup>95</sup>	19	7003	Placebo	+
Opioids <sup>2,18,66,67,71,74,75,98,99</sup>	4	272	Placebo/TCA/lidocaine	3+, 1–
Antidepressants: TCA <sup>2,50,66,68–71,85–90</sup>	7	229	Placebo/lorazepam/other classes of antidepressants	5+, 2–
Topical lidocaine <sup>2,76–78,83,100,101</sup>	6	471	Placebo/pregabalin	+
Topical capsaicin <sup>2,76,79–82,102</sup>	9	1600	Placebo/amitriptyline	7+, 2–
Topical piroxicam <sup>103</sup>	1	18	Placebo/lidocaine	+

**Notes:** + indicates positive outcomes; – indicates negative outcomes.

**Abbreviations:** PHN, post-herpetic neuralgia; TCA, tricyclic antidepressant.

demonstrated a significant efficacy in reducing pain and improving patient quality of life.<sup>96,97</sup>

Although opioid analgesics are accepted as a cornerstone for the treatment of nociceptive and cancer pain, their role in the management of chronic neuropathic pain such as PHN has been debated. The controversy over their efficacy in relieving neuropathic pain reflects the use of multiple definitions and pain assessment methodologies in experimental trials and interindividual differences in opioid responsiveness (Table 2).<sup>67</sup> In addition, many other factors, such as opioid-related side effects, development of tolerance, exaggerated fear of addiction, and differences in governmental health policies, contribute to such a controversy.<sup>67</sup> In spite of that, opioids may be considered as a part of a comprehensive plan for the treatment of PHN,<sup>2,18,71,74</sup> when pain is moderate to severe, with significant impact on quality of life after proven inefficacy of first-line agents. Among the investigated formulations, oxycodone, morphine, fentanyl, buprenorphine, methadone, and weaker opioids such as dihydrocodeine and tramadol were found to be effective. Treatment should be started with a short-acting opioid, replaced after 1–2 weeks with a long-acting formulation (controlled-release morphine, controlled-release oxycodone, methadone, transdermal fentanyl) in the event of insufficient effect. Constipation, nausea, and sedation are common adverse effects associated with opioid use for chronic neuropathic pain. Tramadol has a unique pharmacological profile, which makes it one of the most effective drugs of its class in controlling neuropathic pain, particularly PHN and diabetic neuropathy.<sup>66,98,99</sup> As for side effects, tramadol may cause nausea, vomiting, dizziness, constipation, drowsiness and headache; it also increases the risk of serotonin syndrome in patients using antidepressants such as SSRIs, TCAs, or inhibitors of mono-amino-oxidase in combination.<sup>75</sup>

Local anesthetics may provide analgesia in some neuropathic pain states, where an accumulation of neuronal-specific sodium channels may contribute to pain, including that of PHN.<sup>76</sup> Topical treatments, including lidocaine patches and capsaicin cream/patches, have been studied.<sup>2</sup> Topical adhesive patches containing 5% lidocaine (700 mg) have been used for the treatment of PHN with benefit.<sup>77</sup> Although there are few studies on their efficacy, the available clinical trials in patients with allodynia suggest that lidocaine is effective in providing pain relief with minimal systemic absorption and few side effects, the most frequent being mild skin irritation at the site of application.<sup>78,83,100,101</sup> Capsaicin, the pungent ingredient in hot chili pepper, results in excitation of nociceptive afferents when applied topically. However,

repeated application of capsaicin results in desensitization of unmyelinated epidermal nerve fibers and hypoalgesia.<sup>79,80</sup> Low-concentration (0.025% or 0.075%) capsaicin creams have demonstrated efficacy in the topical treatment of PHN and neuropathic pain conditions.<sup>80</sup> Recently, a high-concentration (8%) synthetic capsaicin dermal patch has been developed with the aim of providing more rapid and long-lasting pain relief after a single application. Banckonja et al<sup>102</sup> evidenced that a one-off application of a high concentration (8%) capsaicin patch for 60 minutes was more effective than a low concentration patch over 12 weeks. Adverse events reported were local reactions at the application site (pain, erythema). Therefore, as evidenced by a Cochrane review, capsaicin, either as a repeated low-dose application of 0.075% cream or even a single application of a high-dose 8% patch, may provide a good degree of pain relief to some patients with painful neuropathic conditions.<sup>81,82</sup>

Other types of topical analgesics that can be applied for the treatment of PHN are currently under investigation. A recent trial evaluated the efficacy of piroxicam patches, resulting in faster and better effects.<sup>103</sup>

## Alternative or adjunctive therapies useful in the treatment of PHN

Six systematic reviews,<sup>67,104–108</sup> four RCTs,<sup>109–112</sup> and one clinical report<sup>113</sup> had evidence relating to this, while no meta analyses did.

A wide variety of interventional options, such as sympathetic and other nerve blocks, intrathecal injections, and spinal cord stimulations, have been analyzed as potential treatments for PHN. Interventional options are part of a comprehensive (invasive and noninvasive) strategy for the treatment of PHN. Selective sympathetic nerve blocks have been one of the most common interventional strategies used.<sup>104,105</sup> The incidence of severe complications from sympathetic nerve blocks is extremely low and, depending on the location of the nerve block, may consist of local anesthetic toxicity, pneumothorax, intraspinal/neuraxial injection, or neurologic injury.<sup>67,106</sup> Some data suggest a link between sympathetic activity and pain in PHN, as patients with PHN demonstrate increased levels of pain and worsening of their allodynia after local administration of adrenergic agonists.<sup>109</sup> Thus, administration of sympathetic nerve blocks may theoretically interrupt the sympathetic-sensory interactions contributing to pain in PHN.<sup>67,105,106</sup> The value of epidural injections for the treatment of existing PHN has not been evaluated.<sup>106</sup> Continuous infusions of analgesic agents (typically an opioid or local anesthetic) via an externalized intrathecal catheter

or an internalized intrathecal pump may also be used for the treatment of PHN, although no controlled trials examining the analgesic efficacy of these modalities are available.<sup>110,111</sup>

In extreme cases, spinal cord stimulation may be effective in the management of severe neuropathic pain.<sup>107</sup> The effects of subcutaneous injections, transcutaneous nerve stimulations, percutaneous nerve stimulations, and radiofrequency on PHN has not been established. There is minor anecdotal evidence for the efficacy of these techniques, and the risk for complications, such as exacerbation of pain, is unknown. There are no controlled studies for any of these interventional procedures.<sup>106</sup> Reported surgical options for PHN include trigeminal or spinal peripheral neurectomy, deep brain stimulation, dorsal root entry zone lesions (DREZotomy), cordotomy, and mesencephalotomy. Microsurgical DREZotomy may interrupt small nociceptive fibers and neurons in the dorsal horn of the spinal cord. General indications for this procedure include well localized pain, neuropathic pain including PHN, and excessive spasticity associated with severe pain. The role of these invasive surgical treatments in the management of PHN is uncertain, as there are no controlled studies to date.<sup>67</sup>

A number of other therapies have been explored, such as N-methyl-D-aspartate receptor antagonists, topical nonsteroidal anti-inflammatory drugs and TCAs, vincristine iontophoresis, botulinum toxin, minocycline, pulsed radiofrequency, and cryoanalgesia. A recently proposed novel approach consists of scrambler therapy; that is, a novel approach to pain control that attempts to relieve pain by providing “non-pain” information via cutaneous nerves, to block the influx of pain information.<sup>112</sup> There is, however, little evidence that justifies evaluation of the efficacy of these therapeutic options.

Acupuncture is another option to treat PHN. A clinical report,<sup>113</sup> the only one to date retrievable in English on the possible role of acupuncture in PHN, lacks sufficient methodological consistency to be quoted in terms of efficacy. A current Cochrane project, however, is due in the near future on this topic.<sup>108</sup>

Neuropathic pain reduces quality of life, including mood and physical and social functioning. Depression and pain-coping strategies, such as catastrophizing and social support, predict pain severity in chronic pain states. Therefore, the importance of psychosocial support and long-term follow-up for severe cases should not be overlooked, as sometimes it is the final tool on which to resort for otherwise intractable cases.<sup>67</sup>

## Discussion

As current evidence shows, treatment for PHN often needs a combination of drugs to achieve the best individual pain

relief, pain management specialists should play a pivotal role in caring for this relatively rare but disrupting condition, aided by infectious disease specialists and general practitioners.

Recent guidelines on evidence-based management of neuropathic pain and PHN provide distinct recommendations for first- and second-line treatment, including possible drug combinations for each step. Guidelines from the European Federation of Neurological Societies<sup>68</sup> recommend TCAs or gabapentin/pregabalin as first-line treatment in PHN (level A). Pregabalin and gabapentin got the same level of evidence, in spite of different safety profiles and convenience. However, both drugs share a remarkable latency to adequate pain relief (up to 4–6 weeks). Topical lidocaine (level A; less consistent results), with its excellent tolerability, may be considered for a first-line approach in the elderly, especially if there are concerns regarding the CNS side effects of oral medications and pain is sufficiently localized. In such cases, a trial of 2–4 weeks is justified. Strong opioids (level A) are recommended as a second choice. Opioids and tramadol are considered as second-line drugs because of their important side effects; they can provide, however, immediate pain relief. Capsaicin formulations are promising (level A), but the long-term effects of repeated applications are not well described, particularly on sensation.<sup>68,102</sup> Other antiepileptic drugs (valproate) may be associated in patients with inadequate pain relief or intolerance to previously indicated medications.<sup>96,97</sup>

A short antiviral course may be efficacious in reducing PHN intensity and duration when a persistent or relapsing ganglionitis may be postulated as the cause of PHN. Alternative therapies such as acupuncture may still be considered.

## Conclusion and future directions

Treatment of PHN is still unsatisfactory in a remarkable proportion of patients, with a considerable economic burden and impact on quality of life. Treatment should be guided by individual pain relief, start as a monotherapy, and progress to include other drugs, possibly with different mechanisms of action. Special care should be addressed to elderly patients on other medications, as side effects and drug-drug interactions may be more common. In patients with inadequate response or intolerance to current treatments, even a small degree of adjunctive pain relief with newer or alternative therapies may be worth considering. Population-based programs for vaccination of elderly (and possibly younger adults) for HZ appear at present the best preventive approach. Timely antiviral treatment of HZ may likely be another tool for prevention, especially for those patients with multiple predictors of PHN at the onset of HZ.



## Further reading

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## Disclosure

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