Management of herpes zoster and post-herpetic neuralgia now and in the future

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SUMMARY

Herpes zoster (HZ; shingles) – a reactivation of the latent varicella zoster virus (VZV) – can cause significant morbidity. Its major complication is pain, particularly post-herpetic neuralgia (PHN). We will review the current management strategies available for the treatment of both acute HZ and PHN, including antiviral drugs, analgesic agents, anticonvulsants, tricyclic antidepressants and topical therapies. New molecules in development that show improved activity against VZV are also covered, and new drug targets are outlined. The role of translational neuroscience in moving towards a goal of finding disease-modifying treatments will be examined.

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Abbreviations

HZ: herpes zoster
PHN: post-herpetic neuralgia
VZV: varicella zoster virus
GP: general practitioner
5-FU: 5-fluorouracil
TTP: thrombotic thrombocytopenic purpura
HUS: haemolytic-uraemic syndrome
FDA: Food and Drug Administration
ZAP: zoster-associated pain
RR: risk ratio
DPD: dihydropyrimidine dehydrogenase
BCNA: bicyclic nucleoside analogue
SVV: simian varicella virus
BPDU: bromovinyldeoxyuridine
HPMPA: 9-(S)-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine
PMEA: phosphonomethoxy-ethyl-adenine
TK: thymidine kinase
TCA: tricyclic antidepressant
ECG: electrocardiogram
DRG: dorsal root ganglion
PRF: pulsed radio frequency
NE: norepinephrine
APN: aminopeptidase N
NEP: neutral endopeptidase
CNS: central nervous system

1. Introduction

The objectives of treating herpes zoster (HZ) are to control acute pain, accelerate rash healing, minimize complications and reduce the risk of post-herpetic neuralgia (PHN) and other late-appearing sequelae. An additional objective, particularly important for immunosuppressed patients, is to reduce the risk of cutaneous and visceral dissemination of the varicella zoster virus (VZV).

2. Current management of acute HZ

The diagnosis of HZ is generally evident at clinical presentation. However, there are situations where diagnosis is difficult, or the patient or physician had not recognized the symptoms and signs early enough. Several studies indicate potential hurdles in diagnosis. One seminal study tested the hypothesis that vaccination against VZV would decrease the incidence and/or severity of HZ and PHN among adults aged >60 years, including the burden of illness. This study involved >38,000 volunteers and demonstrated that 5–6% of the clinical diagnoses by academic physicians were not laboratory confirmed, suggesting that even knowledgeable infectious diseases clinicians are occasionally wrong in their diagnosis. Similarly, a prospective study of HZ diagnoses by general practitioners (GPs) found 17% of diagnoses to be incorrect.

Furthermore, in a recent study of psychosocial correlates of HZ, which used pain as an indicator of disease onset, 92% of 533 individuals with HZ had pain at presentation. However, only 46% sought medical attention within 72 hours of pain onset and 54% within 72 hours of rash appearance. Initial assessment was late, at a median time of 72 hours after the onset of rash. Importantly, >80% of the subjects reported prodromal pain, which in the majority of cases lasted 2 or 3 days.
studies used a wide range of definitions, including 'any pain that of acute zoster until its complete resolution, if it occurs. pain (ZAP), whereby pain is viewed as a continuum from the time after skin healing. The third form of pain is that of zoster-associated after disease onset’. PHN is defined by the US Food and PHN have been used over the past 30 years, and all have different implications for clinical studies. Second, and follows disappearance of the rash of herpes zoster’, whereas other studies used the definition of ‘pain present for more than 1 or 2 months after rash onset’. However, recent models of pain resolution and statistical analysis suggest that the most appropriate definition of PHN is pain that persists 90 days or more after the onset of HZ rash.

In early acyclovir studies, PHN was defined as ‘persistence 30 days after disease onset or the healing of skin’. Thus, the early acyclovir trials and a large meta-analysis involving 691 patients suggested that acyclovir (800 mg five times daily for 7–10 days) was more effective than placebo in reducing pain. Benefits were particularly noticeable for patients aged >50 years. Overall, the incidence and duration of PHN among patients receiving acyclovir were half those reported by placebo recipients, and fewer acyclovir-treated patients had PHN at 3 and 6 months. However, this has not been proven in a sufficiently powered prospective study.

According to ZAP analyses from various clinical studies, valacyclovir (a prodrug of acyclovir) is more efficacious than acyclovir. One study comparing two different regimens of valacyclovir (1000 mg three times daily for 7 days, or 1000 mg three times daily for 14 days) with acyclovir (800 mg five times daily for 7–10 days) showed that the time to ZAP resolution was significantly longer with acyclovir therapy (median time to ZAP resolution: acyclovir, 14 days) with acyclovir (800 mg five times daily for 7–10 days) was more effective than placebo in reducing pain. Benefits were particularly noticeable for patients aged >50 years. Overall, the incidence and duration of PHN among patients receiving acyclovir were half those reported by placebo recipients, and fewer acyclovir-treated patients had PHN at 3 and 6 months. However, this has not been proven in a sufficiently powered prospective study.

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group; HR 1.17; CI 0.98–1.39; \( p = 0.09 \) for the 14-day valacyclovir group). In this study, pain was recorded in 85% of the patients in the acyclovir group, and in 79% and 80% of the patients receiving valacyclovir for 7 and 14 days, respectively.

Famciclovir is also an effective and well-tolerated therapy of HZ. A study of 419 patients with HZ given either famciclovir 500 mg/day or 750 mg/day for 7 days, or placebo, showed that famciclovir treatment accelerated lesion healing and decreased the median duration of PHN resolution.\(^{14}\) The efficacy-evaluable analyses revealed that time to full crusting was 1.3- to 1.5-fold faster in the 500 mg famciclovir (\( p = 0.02 \)) and 750 mg famciclovir (\( p = 0.02 \)) groups compared with the placebo group. PHN was also significantly reduced in the famciclovir groups (500 mg famciclovir: HR 1.7 and 95% CI 1.1–2.7; 750 mg famciclovir: HR 1.9 and CI 1.2–2.9; \( p = 0.02 \) and 0.01, respectively).

Famciclovir has the advantage of reduced frequency of dosing\(^{15,16}\) but it is important to note that the recommended dose of famciclovir varies between countries. A study of 545 patients with HZ randomized to receive 7 days of either famciclovir 250, 500 or 750 mg three times daily or acyclovir 800 mg five times daily, initiated within 72 hours of the onset of the zoster rash, showed that famciclovir was as effective as acyclovir at all doses for the healing of cutaneous lesions.\(^{17}\) Time to resolution of acute pain was similar in all arms, but time to ZAP resolution was significantly shorter in those treated with famciclovir within 48 hours of rash onset compared with acyclovir (famciclovir 250, 500 and 750 mg vs. acyclovir, \( p = 0.006, 0.003 \) and 0.042, respectively).\(^{17}\) Median time to ZAP resolution after skin healing was faster in the famciclovir arms than in the acyclovir arm (resolution was 1.4 \( p = 0.086 \), 1.8 \( p = 0.003 \) and 1.4 \( p = 0.05 \) times faster in the 250 mg, 500 mg and 750 mg famciclovir groups, respectively, compared with acyclovir).\(^{17}\)

A direct head-to-head comparison of famciclovir and valacyclovir in immunocompetent patients aged >50 years showed that the two drugs were therapeutically equivalent, for both healing rate and pain resolution.\(^{18}\)

The fourth commercially available anti-VZV drug used to treat HZ is the synthetic pyrimidine analogue, brivudin. Brivudin is licensed in some European countries, South Africa and Israel for the early treatment of HZ in immunocompetent adults.\(^{19}\) Brivudin is 200–1,000 times more effective in inhibiting viral replication in vitro than acyclovir or penciclovir;\(^{20}\) and it accumulates rapidly inside virus-infected cells.\(^{21}\)

Brivudin (125 mg once daily for 7 days) was more effective than acyclovir (800 mg five times daily for 7 days) in a study of 1,227 immunocompetent patients with HZ.\(^{22}\) The time to ZAP resolution was similar between the two groups (risk ratio [RR] 0.996; \( p = 0.001 \)), but the brivudin group had a faster time to last formation of new vesicles compared with acyclovir (RR 1.13; \( p = 0.014 \)). However, the intent-to-treat analysis of lesion healing indicated that brivudin is as effective as acyclovir according to time to first crust (brivudin RR 0.93; 95% CI 0.83–1.05; acyclovir RR 0.93, CI 0.83–1.05), time to full crusting (brivudin RR 1.03; 95% CI 0.92–1.16; acyclovir RR 1.03, CI 0.92–1.16) and time to loss of crusting (brivudin RR 0.95; 95% CI 0.85–1.07; acyclovir RR 0.93, CI 0.85–1.07). A large multicentre study of 2,027 patients with acute HZ aged ≥50 years demonstrated that brivudin had a similar efficacy on pain and rash and a similar tolerability profile to famciclovir (250 mg three times daily for 7 days).\(^{23}\)

Drug interactions have been reported between brivudin and 5-FU and other 5-fluoropyrimidines. The main metabolite of brivudin, bromovinyl uracil, inhibits dihydropyrimidinase dehydrogenase (DPD), which regulates the metabolism of pyrimidine derivatives; hence, brivudin therapy can cause the accumulation and enhanced toxicity of these drugs. A congener analogue, bromovinyl arabinosyl uracil (BVArA), when administered to patients receiving 5-FU, resulted in several deaths in Japan.\(^{24}\) Consequently, brivudin should not be administered concomitantly with 5-FU or its derivatives, capecitabine, flouxuridine or flucytosine. As a further precaution, DPD activity should be monitored before starting any treatment with 5-fluoropyrimidine drugs in patients who have recently received brivudin.\(^{25}\)

2.2. The rationale for existing antiviral treatment schedules

Current evidence from clinical trials is based on the initiation of therapy within 72 hours of rash outbreak.\(^{26}\) There are no well-controlled clinical trials that have compared early-onset therapy with later therapy (>72 hours). Bean et al.\(^{27}\) found that the time to viral shedding was reduced by acyclovir therapy compared with placebo in patients who had a zoster rash for <72 hours (Figure 1). It is surprising that, in a HZ vaccine trial,\(^{25}\) only two thirds of the patients who developed HZ received appropriate antiviral treatment within 72 hours, despite being informed at study onset about the symptoms and signs of HZ. These drugs may afford greater benefit if they are used within the first 72 hours of rash onset. Early diagnosis and treatment of HZ result in accelerated cutaneous healing and reduced median duration of pain according to the ZAP analyses. It seems likely that one of the major causes of decreased efficacy of antiviral therapy is the delay between onset of symptoms and initiation of treatment. Treatment with more active and lipophilic agents may be beneficial in reducing viral replication and consequent neural damage as quickly as possible, and hence may reduce both acute and chronic manifestations of HZ. The need for more education of the public and healthcare providers on HZ is also evident.

![Fig. 1. Time to cessation of viral shedding.\(^{27}\) Reprinted from Bean B, et al., Acyclovir therapy for acute herpes zoster. Lancet 1982;320(8290):118–21. © 1982, with permission from Elsevier.](image-url)
outcome at 5 or 10 years than non-treated patients (2.1% vs. 8.9%, respectively, \( p = 0.009 \)). Furthermore, the development of serious inflammatory complications among treated patients appeared to be associated with a delay in antiviral treatment, which emphasizes the importance of early treatment. The concomitant treatment with corticosteroids under the supervision of an ophthalmologist is discussed here.

Current International Herpes Management Forum (IHMF®) guidelines\(^{30}\) recommend that all patients with zoster ophthalmicus presenting within 1 week of rash onset should be offered oral antiviral therapy with one of the following to reduce the incidence of ocular complications: (a) acyclovir 800 mg five times daily for 10 days; (b) valacyclovir 1000 mg three times daily for 7 days; or (c) famciclovir 500 mg three times daily for 7 days.

2.3. The role of corticosteroids

When administered systemically within 72 hours of rash onset, corticosteroids have a clinically significant benefit on acute pain but no demonstrable effect on PHN.\(^{28,32}\) A double-blind study of 400 acute zoster patients, comparing oral acyclovir (800 mg five times daily) with and without prednisolone, found that more of the rash area had healed on Days 7 and 14 (\( p = 0.02 \)) in those receiving steroids.\(^{28}\) Pain reduction was greater during the acute phase of the disease in those treated with steroids than in those without steroids. However, there were no significant differences between any of the groups in the time to first or complete cessation of pain. Notably, no placebo controls were included in this study.\(^{28}\)

There is evidence that the use of steroids in combination with acyclovir can improve quality-of-life outcomes in healthy patients aged >50 years with localized HZ.\(^{22}\) More than 200 patients with acute HZ were stratified into four arms to receive acyclovir or placebo plus prednisone or placebo during the acute phase of their illness. Times to total crusting and healing were accelerated in patients receiving acyclovir plus prednisone compared with patients receiving two placebos; patients receiving acyclovir plus prednisone had a shorter time to cessation of acute neuritis, time to return to uninterrupted sleep, time to return to usual daily activity and time to cessation of analgesic therapy. However, there was no difference in pain resolution during the 6 months after rash onset between the combination therapy group and the other groups. Individuals at risk for complication of steroid therapy were excluded from this trial (e.g., those with hypertension, osteoporosis and/or diabetes, among others).\(^{32}\)

If there is any evidence of uveitis or corneal inflammation, topical ophthalmic steroids are prescribed by ophthalmologists in combination with an oral drug for zoster ophthalmicus. Systemic steroids are routinely considered in patients with HZ who have added symptoms from the compression of enlarged, inflamed nerve roots, such as in VII nerve palsy.

2.4. New molecules in development

Four new drugs are being considered for the treatment of HZ: CMX001, a nucleoside analogue valomaciclovir (H2G); a helicase-primase inhibitor; and two bicyclic nucleoside analogues (BCNAs).

CMX001 (hexadecyloxypropyl-cidofovir) is a lipid ester of cidofovir with enhanced oral bioavailability conferred by the lipid moiety. The enhanced bioavailability of the ester also reduces nephrotoxicity by reducing exposure to cidofovir.\(^{33}\) Once inside the cell, the molecule is cleaved by phospholipase to liberate cidofovir.

In cell culture assays, CMX001 is significantly more active than cidofovir against all double-stranded DNA viruses, including VZV and other herpesviruses.\(^{34}\) Because it is a derivative of and is metabolized to cidofovir, there is a persistent concern for its toxicity, and in particular its carcinogenicity.\(^{35}\) Importantly, in Phase IB and early Phase II studies, nephrotoxicity has not been a concern. It is envisioned that CMX001 will have a primary role in the organ transplant setting.

Valomaciclovir is the diester prodrug (valine and stearic acid) of the acyclic guanosine derivative. H2G. It is a potent, broad-spectrum anti-herpes agent, especially active against VZV infection, and is phosphorylated by virus-infected cells to H2G triphosphate to yield a potent inhibitor of viral DNA synthesis. The pre-clinical pharmacology and toxicology, initial human clinical pharmacology and pharmacokinetics, and Phase II proof-of-efficacy of valomaciclovir have now been completed.\(^{36}\)

Helicase-primase inhibitors prevent viral DNA replication by inhibiting VZV-specific enzymes. The helicase-primase inhibitor ASP2151 is more potent against VZV than acyclovir in tests against several strains of the virus, including clinical isolates.\(^{37,38}\)

The aryl BCNAs are extremely potent and selective against VZV. The lead molecule, Cf1743 (Figure 2),\(^{39}\) shows activity at around 0.1 nM in vitro, making it 10,000 times more potent than acyclovir. The BCNAs are also highly selective; whereas other nucleoside analogues have activity against simian varicella virus (SVV), the BCNAs are inactive against SVV. Moreover, SVV has a genome sequence that is 75% homologous to VZV and shares many common features, including latency, recurrence and varicella-like disease. All previous compounds that inhibit VZV also inhibited SVV, the ratio of \( EC_{50} \) values (SVV:VZV) being 0.2:7 among the diverse families of antivirals, including bromovinydeoxygenuridine (BVDU), BVaraL, acyclovir, ganciclovir, penciclovir, 9-(S)-[3-hydroxy-2-(phosphonomethoxy)propyl]adenine (HPMPA) and phosphonomethoxy-ethyl-adenine (PMEA).\(^{40}\) Therefore, the BCNAs are the first compounds shown to inhibit VZV while being inert to SVV. This result cannot be explained by lack of phosphorylation.
because the BCNAs are competitive inhibitors; also, alternative substrates for the SVV include thymidine kinase (TK), therefore BCNA nucleotides must arise in SVV-infected cells.

BCNAs are non-toxic in vitro and have no toxicity up to very high doses (2000mg/kg) in vivo. They are highly lipophilic and rapidly permeate cell membranes. Whereas the parent compounds have poor water solubility and low oral bioavailability, these problems are both solved by esterification, resulting in the valyl produgh FV100. FV100 is currently under development, having successfully completed Phase I clinical trials in the USA; Phase II studies in HZ are ongoing.40

3. PHN and other complications

HZ is associated with significant neurological complications, the most prevalent being pain (see Gershon et al., this supplement,42 and Opstelten et al., this supplement43).

3.1. The limitations of antiviral therapies in PHN

While antiviral drugs are clinically effective in the treatment of acute HZ, the data about their benefit in reducing the duration of or incidence of PHN are conflicting. The incidence of PHN in selected clinical trials is summarized in Table 2. A meta-analysis of all placebo-controlled trials with acyclovir for HZ established that there is a significant reduction in ZAP in patients who received acyclovir.46 Similar results were obtained with valaciclovir (ZAP analysis), which is also more effective than acyclovir at reducing the duration of PHN11; the average duration of pain was 38 days with valaciclovir and 51 days with acyclovir. Similar reductions in pain were also noted at 6 months after healing of the rash; only 19% of patients taking valaciclovir reported pain compared with 26% of patients taking acyclovir.11 However, a recent Cochrane report47 concluded that acyclovir has no effect on PHN, although the study design determined which studies were included in the review – and many were excluded. The Cochrane report noted that pain severity, in addition to pain duration, should be used as an efficacy measure in future randomized trials of antivirals for the prevention of PHN.47

Famiclovir has also proven effective in acute HZ, promoting cutaneous healing and reducing the duration of acute pain. The median duration of pain was half as many days in patients who received famiclovir compared with those receiving placebo, resulting in a 3.5-month reduction in the average duration of pain.15 When famiclovir and valaciclovir were compared in a head-to-head study, the drugs were equally effective at resolving ZAP.18

Complications of HZ other than PHN are poorly studied, and reliable epidemiological information is scarce. An observational, retrospective analysis of 1,401 HZ cases recorded by dermatologists and GPs in Italy showed that the most frequently occurring zoster-related complications, excluding PHN, were ocular complications (5.7%), arthritis (0.7%) and facial palsy (0.6%), with the risk increasing with age.42 Individuals aged >65 years had almost four times the risk of complications as those aged <35 years. Interestingly, much lower rates of zoster complications were observed in the recent Shingles Prevention Study.2 The most frequent zoster-related complications, excluding pain, were neurological (1.4%) and ocular (0.7%) in non-vaccinated individuals, and cutaneous (0.7%) and neurological (0.5%) in vaccine recipients.2 Ocular complications were markedly lower in this North American population than in Italian clinical practice, which could be attributed to the prompt use of antiviral drugs for the majority of patients.48,49 However, it could also reflect regional variations, differences in study selection criteria or some other unidentified cause, such as concurrent use of biological therapies (e.g., the monoclonal antibodies infliximab and adalimumab or the fusion protein etanercept used to treat autoimmune diseases such as rheumatoid arthritis), which appear to have an effect on the incidence, severity and type of HZ. A disproportionately high incidence of atypical and severe presentations occurs in patients receiving biological therapies.50,51

3.2. Other treatments for PHN

Opoid analgesics are frequently prescribed for the treatment of acute and persistent pain. Both short- or long-acting agents, such as controlled-release morphine and oxycodone, may be used.52 The side effects of opioid analgesics include drowsiness and cognitive slowing, nausea, constipation and pruritus. General concerns about the potential for abuse are less relevant for geriatric populations, particularly in older patients with no previous history of substance abuse. In a blinded, within-patient, crossover trial comparing opioids, tricyclics and placebo for established PHN, opioids had the highest patient preference.53

Tricyclic antidepressants (TCAs) and the anticonvulsants gabapentin and pregabalin have been the most frequently studied drug classes for the management of neuropathic pain, including PHN.54 TCAs provide moderate to excellent pain relief and have been used extensively for the treatment of PHN.55,56 They are widely available in generic form and can have added benefits for mood and sleep. In a retrospective study to assess the effects of acyclovir treatment of acute HZ on subsequent PHN, the effect of amitriptyline was also examined; early treatment was almost twice as likely to be successful as late treatment.57 Amitriptyline is the most widely prescribed TCA for PHN, but others, such as nortriptyline and desipramine, can also be used effectively and may have fewer side effects.58 Side effects associated with amitriptyline are common and include cardiovascular problems such as orthostatic hypotension,

Table 2

Prevalence of PHN at 6 months in selected clinical trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion of patients with pain (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir (800mg five times daily) vs. placebo for 7 days</td>
<td>14 vs. 13</td>
<td>McKendrick et al., 198945</td>
</tr>
<tr>
<td>Acyclovir (800mg five times daily for 7 days) vs. placebo</td>
<td>15 vs. 250a</td>
<td>Morton and Thomson, 198944</td>
</tr>
<tr>
<td>Valaclovir (1000mg three times daily for 7 or 14 days) vs. acyclovir (800mg five times daily for 7 days)</td>
<td>19.3 vs. 25.7a</td>
<td>Beutner et al., 199513</td>
</tr>
<tr>
<td>Valaclovir (1000mg three times daily for 7 days) vs. acyclovir (1000mg three times daily for 14 days)</td>
<td>19.9 vs. 18.6a</td>
<td>Beutner et al., 199513</td>
</tr>
<tr>
<td>Famiclovir (500 or 750mg three times daily) vs. placebo for 7 days</td>
<td>Approximately 20 vs. 40a</td>
<td>Tyring et al., 199517</td>
</tr>
<tr>
<td>Valaclovir (1000mg three times daily) vs. famiclovir (500mg three times daily) for 7 days</td>
<td>19 vs. 19a</td>
<td>Tyring et al., 200014</td>
</tr>
<tr>
<td>Brivudin (125mg once daily) vs. famiclovir (250mg three times daily) for 7 days</td>
<td>11.3 vs. 9.6ab</td>
<td>Wissel et al., 200523</td>
</tr>
<tr>
<td>Brivudin (125mg once daily) vs. acyclovir (800mg five times daily) for 7 days</td>
<td>32.7 vs. 43.5ab</td>
<td>Wissel et al., 200322</td>
</tr>
</tbody>
</table>

a p<0.05. b 3-month follow-up.
arrhythmias and electrocardiogram (ECG) abnormalities. These side effects may be an issue when prescribing to elderly patients; hence, either nortriptyline or desipramine is the preferred treatment.

Gabapentin, a second-generation anticonvulsant, significantly reduces the severity of PHN.59,60 Patients receiving gabapentin have lower daily pain scores and fewer disturbances in mood and sleep compared with those receiving placebo.59,60 Although there is no standard dosing regimen, recent studies indicate that treatment can be initiated at 900 mg/day and, if pain relief is not satisfactory, the dose may be titrated to 1800 mg/day as side effects permit (often about 7–10 days).61 Higher doses (up to 3600 mg/day) may be required in some patients. Gabapentin has a good safety profile, especially among older patients. Designed as a more potent successor to gabapentin, the anticonvulsant pregabalin, like gabapentin, is associated with analgesic, anxiolytic and antiepileptic activity.62 Analgesic effects are mediated through the a2-d-3 subunit. Oral bioavailability is ≥90%, and peak blood level is achieved in 1.3 hours with no plasma protein binding. Pregabalin is devoid of drug interactions. Because it is excreted unchanged by the kidneys, it is contraindicated in severe renal impairment (CLcr ≤30).63 Four studies using 150–600 mg/day in divided doses showed efficacy in reducing pain and sleep interference in PHN.64 It is generally well tolerated but may cause side effects similar to those of gabapentin. Pregabalin offers a more rapid clinical effect than gabapentin.

Topical analgesics are commonly used for the relief of PHN, despite very limited evidence of efficacy. Topical agents for the treatment of PHN include: acetylsalicylic acid 500 mg in 95% alcohol 5 mL; lidocaine 5% patch or gel; geranium oil65; and capsaicin.66 Capsaicin cream 0.025%, applied three or four times daily, is commonly prescribed (but rarely tolerated). It reduces pain by activating the TRPV1 receptor and depleting substance P66 leading to subsequent desensitization and drying back of nociceptive axon endings. Side effects include intolerable burning pain, and one meta-analysis showed the efficacy of this therapy to be limited.67 An 8% formula patch of capsaicin following topical local anaesthesia was recently compared with the usual 0.04% capsaicin patch in a randomized controlled trial of 402 patients with PHN.68 One 60-minute application of the 8% capsaicin patch provided rapid and sustained pain relief, with 42% of patients experiencing >30% pain relief compared with 32% of patients in the 0.04% capsaicin patch group (Figure 3). Actual benefit and tolerability of the capsaicin patch in clinical practice remain to be determined, as does the long-term effect on axonal damage.

A topical 5% lidocaine patch can also provide PHN relief for approximately 12 hours after application, with no or mild side effects.69 Both oral gabapentin and the lidocaine patch, as well as pregabalin, are approved by the FDA for the treatment of PHN and may be considered as first-line treatments.

Alternative therapies for the relief of PHN, and methods of less-certain efficacy, include:

- Invasive techniques, such as nerve blocks, intrathecal administration of local anaesthetics and excision of the affected skin
- Neuromodulation techniques
- Toxins such as BOTOX-A®
- Combinations of drugs
- Pain management programmes.

Nerve blocks are often used by anaesthesiologists in pain clinics for the treatment of HZ, but there are no controlled clinical studies demonstrating their efficacy. The rationale for sympathetic blockade is particularly problematic as the sympathetic ganglia are spared from acute HZ involvement. Nerve-block interventions can target several sites, such as the dorsal root ganglion (DRG), peripheral nerves, sympathetic chain and epidural blocks. A recent study of epidural steroid injection failed to show that this approach provided any benefit in preventing long-term PHN. A single epidural injection of steroids and local anaesthetics during the acute phase of HZ modestly reduced pain for 1 month (ZAP analysis),70 but the benefit was lost by 3 months post-treatment. Treating PHN with a single injection near a single DRG is not always advisable as it can be difficult to tell precisely which dermatome is affected. Prognostic nerve blocks may need to be performed to identify the correct ganglion, and there are no data to support the efficacy of this invasive treatment. The intrathecal administration of local anaesthetics, corticosteroids and neuroactive peptides is another potential therapy. In a trial comparing lidocaine with lidocaine and methylprednisolone,71 the combination of lidocaine and methylprednisolone administered in weekly injections over 4 weeks decreased the intensity and area of pain and reduced the use of the non-steroidal anti-inflammatory drug diclofenac compared with either lidocaine alone or no treatment. One year after treatment, 82% of patients in the lidocaine and methylprednisolone group reported good or excellent pain relief compared with only 5% in the lidocaine-only group. Despite the promising results from this trial, intrathecal steroid injections have not become widely used for the management of PHN, mainly owing to concerns over safety and the lack of confirmation or verification in clinical practice.

Neuromodulation refers to a group of techniques that stimulate various parts of the nervous system to relieve pain. Limited data support the use of implanted spinal cord stimulators for PHN. A single study reports that pulsed radio frequency (PRF) ablation of the DRG provided significant pain relief compared with conventional pain treatments in patients with intractable PHN.72
There is limited evidence concerning efficacy of stimulation. Medically unresponsive PHN affecting the face or hand is a reasonable target for motor cortex stimulation, a minimally invasive option in which electrodes are placed outside the brain. A meta-analysis of 11 studies using non-invasive brain stimulation and 22 studies using invasive brain stimulation showed that brain stimulation of the motor cortex can have a significant effect on chronic pain, with responder rates of 73% in the invasive stimulation studies and 45% in the non-invasive stimulation studies. Such treatments are rarely indicated.

3.3. New drug targets for PHN

Many targets for drugs in the pain pathway have been identified, indicating the complexity of pain pathways and the inability to identify one key target. Among the candidates being assessed are:

- TRPV1 receptor, which has been targeted by many drugs, including capsaicin
- NMDA receptor; drugs targeting this receptor have not been found to be effective in the treatment of PHN
- Cannabinoids have been tested in studies, but they are unlikely to be used in the clinic because of their legal status in the USA
- Calcium channels are targeted by pregabalin and gabapentin, but there are other subunits of the channel that could represent therapeutic targets
- Sodium channels are the targets for many antiepileptic drugs, some of which have been tested in PHN with only minimal efficacy
- The norepinephrine (NE) transporter is a new target, and drugs that interact with this molecule are still at Phase I of development
- Drugs that target the aminopeptidase N (APN) and neutral endopeptidase (NEP) are still in early phases of research
- Neurotrophic factors and growth factors are potentially interesting targets because it is thought that the loss of nerve fibres plays an important role in the pathogenesis of PHN.

3.4. Managing PHN in the future: Translational neuroscience

The goal for managing PHN in the future will be to move away from palliative care towards disease-modifying treatments. Identifying patients at highest risk of developing PHN might permit the development of new translational therapies to be used early in the disease. Surrogate markers obtained from skin biopsy data might enable early identification of HZ patients at high risk for PHN, e.g., vibration threshold measurements using graduated tuning forks or laser Doppler measurements of skin blood flow.

An important advance in the understanding of the pathogenesis of PHN was the documentation of the loss of neurites in the skin during HZ (Figure 4). It is known that there is a step-function relationship between axonal degeneration and the presence of PHN pain, and a threshold of 650 neurites/mm² dichotomizes HZ patients with or without PHN. This implies that the absence of pain after HZ may require the preservation of a minimum density of primary nociceptive neurons. Because virtually all axons that end in the epidermis are nociceptors, the loss of nociceptive input from the skin into the central nervous system (CNS) may contribute towards maintaining ongoing pain. Similar mechanisms contribute to phantom limb pain after amputation. The plasticity of the nervous system is becoming better understood, particularly the way in which near-normal function can be maintained in some degenerative conditions (including Parkinson's disease, optic nerve crush, spinal cord injury and stroke) despite the degeneration of many neurons. After injury, post-synaptic neurons adapt to enlarge capacity by increasing their gain – a strategy that can ultimately lead to unprovoked firing of central neurons when peripheral input is reduced to near zero. If this also applies in PHN, the implication is that even small reductions in neuronal death might preserve the minimal necessary residual number of neurons and thereby decrease the likelihood of PHN. A better understanding of this pathophysiology will inform the development of therapeutic and preventative strategies for PHN and other chronic pain syndromes.

Other observations of the CNS and nerve injury may provide insight into chronic pain syndromes. For example, unilateral nerve injury from HZ can cause profound, long-lasting, nerve-branch-specific loss of dorsal-horn neurones, perhaps providing a biological correlate for the disproportionate pain of post-traumatic neuralgias that follow seemingly minor nerve injuries. Animal research shows that minor nerve injuries can have disproportionately large effects on dorsal-horn neurons and glia, perhaps providing a biological correlate for the disproportionate pain of post-traumatic neuralgias that follow seemingly minor nerve injuries.

Animal research shows that minor nerve injuries can have disproportionately large effects on dorsal-horn neurons and glia, perhaps providing a biological correlate for the disproportionate pain of post-traumatic neuralgias that follow seemingly minor nerve injuries. It is well documented that reduced nociceptive afferent input causes hyperactivity of central pain neurons and limited autopsy data comparing patients with or without HZ after HZ identified degeneration in the spinal-cord dorsal horn as the crucial difference between these outcomes.

4. Summary

The objectives of treating HZ are to control acute pain, accelerate rash healing, minimize systemic complications and reduce the risk of PHN and other complications. Existing therapies, particularly antiviral agents, shorten the duration of HZ and promote rash healing, but they are not completely effective at preventing PHN, perhaps partly because of delays in diagnosis and administration. New treatments with different mechanisms of action are under development for the prevention and management of PHN. Existing therapies for established PHN are palliative and mainly include...
opioids, TCAs and anticonvulsants. The goal for PHN management in the future must be to move away from palliative care and towards disease-modifying treatments. Recent developments in the understanding of the neuropathogenesis of pain in general, and of PHN in particular, have identified potential points of intervention for the future management of chronic pain syndromes, including PHN.

Conflict of interest
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