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# Tolerability of Treatments for Postherpetic Neuralgia

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## Contents

## Abstract

Herpes zoster occurs in up to 20% of people infected with varicella-zoster virus, due to reactivation of the virus from latently infected sensory ganglia. Although pain is a typical feature of acute zoster, pain persisting for more than a month after resolution of the rash is less common and is termed postherpetic neuralgia (PHN). The pain associated with PHN is neuropathic in origin and is notoriously difficult to treat. The incidence of herpes zoster and its associated complications both increase with age, so PHN should be seen more commonly in an aging population.

Vaccination with live, attenuated varicella vaccine is safe and efficacious, particularly in children. It decreases the incidence of acute varicella and subsequent herpes zoster. Aciclovir is well tolerated, with renal toxicity only at high intravenous doses. Treatment of acute varicella with aciclovir attenuates acute illness but does not prevent herpes zoster. Treatment of herpes zoster with aciclovir or its derivatives minimises symptoms and may reduce the rate of PHN. Foscarnet is an alternative for an aciclovir-resistant virus but its use is limited by renal and CNS toxicity. Corticosteroids reduce acute pain in herpes zoster but do not affect the incidence of PHN. Their use in some patients may be limited by adverse effects such as gastritis and impaired glucose tolerance.

Treatment of established PHN is difficult and may require a holistic approach. Tricyclic antidepressants and gabapentin are the systemic agents with the most proven benefit, although opioids such as oxycodone and NMDA receptor antagonists such as ketamine may be useful in some people. Adverse effects from tricyclic antidepressants are common but usually mild, while gabapentin is generally well tolerated. Although effective, the relatively common adverse effects of opioids and ketamine limit their usefulness in treating PHN. Topical treatment with 5% lidocaine patch or capsaicin is of benefit in some patients and is generally well tolerated. Intrathecal methyl prednisolone may be considered for intractable pain but efficacy and safety have not been confirmed.

Varicella-zoster virus (VZV) is a human alpha herpesvirus that establishes latent infection in sensory ganglia. Primary infection occurs most commonly in childhood, presenting clinically as varicella (chicken pox). In children with normal immune systems the infection is usually self-limiting and results in lifelong humoral immunity. The most common long-term complication of VZV infection is herpes zoster (shingles), which causes significant acute and chronic morbidity, particularly in older individuals. The most feared complication of zoster is postherpetic neuralgia (PHN), a major cause of chronic pain. This article provides an overview of research aimed at preventing or treating PHN, focusing in particular on the comparative tolerability of treatment options.

## 1. Epidemiology

### 1.1 Varicella

Primary varicella (chickenpox) is predominantly a childhood disease, especially in temperate countries. Ninety percent of cases in the US occur in children aged <13 years, with only 10% of people aged >15 years considered susceptible to infection.[1] The pattern is different in tropical countries, with approximately 50% of the people in Singapore acquiring varicella by the age of 24 years.[2] Transmission is presumed to occur via the respiratory route, with intimate contact important.[1]

### 1.2 Herpes Zoster

Herpes zoster (shingles) follows the reactivation of a latent virus from the dorsal root or trigeminal sensory ganglion of a previously infected individual. There is an estimated 20% lifetime risk of developing zoster, most often in later years.[1] The incidence is equal for both sexes.[3] The risk of reactivation increases with age; the annual incidence is 0.4–1.6 cases per 1000 in healthy people aged <20 years and 4.5–11 cases per 1000 in people aged ≥80 years.[4] Herpes zoster develops eight to ten times more frequently in people aged ≥60 years than in those aged <60 years of age.[5] Most people who develop zoster have only one episode, with the risk of recurrent zoster in immunocompetent people being <5%.[6]

Reduced cellular immune function, which decreases with age, is thought to play a role in VZV reactivation and the development of herpes zoster. Zoster is several times more likely to occur in people with HIV infection or malignancy; leukaemia increases the risk in children by a factor of 50–100 times.[4]

As well as increasing the incidence of zoster, advancing age increases the rate of complications following herpes zoster, as highlighted in a large observational study of 859 individuals with herpes zoster.[7] Compared with patients aged <45 years, the risk of complications doubled in patients aged 45–64 years and was over six times higher in patients aged ≥65 years.

### 1.3 Postherpetic Neuralgia (PHN)

The most common complication of zoster is PHN.[4] Most patients experience pain during acute herpes zoster, which may start before the onset of a skin rash. This pain usually resolves over time, but may persist for months or years and may recur after a pain-free interval. PHN is variably defined as pain persisting from 1 to 6 months after the onset of a rash or after the resolution of a rash, confusing the interpretation of clinical trial data (see below). Some authors prefer to consider all pain as a continuum, i.e. zoster-associated pain. However, both the pathogenesis and nature of acute and chronic pain differ. These issues have been discussed at several expert meetings and the results of the discussions have been published.[8] Here we will continue to refer to PHN as pain that occurs or persists for more than 1 month after the onset of rash.

Depending on the definition, between 10% and 70% of patients with herpes zoster develop PHN. The rate increases with age, with few children developing PHN. Estimated rates of PHN in untreated adults aged >55, >60 and >70 years are 27%, 47% and 73%, respectively. Pain lasting more than 1 year has been reported in 4%, 22% and 48% of patients aged <20, >55 and >70 years, respectively.[4] The severity of this persistent pain has not been defined.

Despite an apparently increasing incidence of herpes zoster because of an aging population, the overall complication rate has remained stable over the last 40 years, ranging from 12% to 14%.[7,9]

Clinical predictors of PHN include older age, prodromal symptoms, severe acute pain, increased number of lesions, connective tissue disease or HIV infection.[10,11] One study investigating potential confounding factors concluded that age, rash severity and acute pain severity, although interrelated, probably reflect different pathophysiological processes and each independently predicts an increased risk of PHN.[12]

An Icelandic study that attempted to quantify pain severity found that only 1.8% of patients aged <60 years reported pain that was mild.[13] Two patients aged >60 years reported severe pain, but this was resolved by 12 months. The reasons for these unusually low rates of post-zoster pain are unclear, but may reflect selection bias, cultural differences or differing methods for reporting and measuring pain.[14]

## 2. Pathogenesis of Varicella-Zoster Virus (VZV) Infection

### 2.1 Primary Varicella

Approaches to the prevention and treatment of PHN depend on an understanding of the pathophysiology of VZV. Humans are the only known host for the virus, which is transmitted via the respiratory

route. The typical 'incubation period' or time from infection to the appearance of vesicular rash is 14 or 15 days (range 10–20 days).[1] Following inoculation of mucous membranes, the virus replicates in the upper respiratory tract or nasopharynx, travels to regional lymph nodes, possibly via infected dendritic cells,[15] further replicates in lymphocytes[16] and then infects the liver and reticulo-endothelial system via a primary viraemia.

A secondary, cell-associated viraemia disseminates virus to cutaneous epithelial cells, probably via peripheral blood mononuclear cells (PBMC), resulting in vasculitis and the typical vesicular rash.[16] Late during incubation, VZV is transported back to the respiratory mucosa.

Patients are infectious from 2 days prior to the onset of a rash and up to 5 days afterwards, with secondary attack rates between 70% and 90%.[1] Virus is detectable in respiratory secretions and vesicular fluid by polymerase chain reaction (PCR).

Resolution of the varicella rash coincides with the onset of humoral and cell-mediated immunity, which is lifelong in the normal host.[16] VZV in immunocompromised individuals may disseminate to involve lungs, CNS, liver and other organs.

### 2.2 Latent Infection and Reactivation

VZV establishes latent infection in the sensory ganglia of the spine or brainstem, either by direct haematogenous seeding or by retrograde axonal spread of the virus from mucocutaneous sites.[16]

Although VZV and herpes simplex virus (HSV) both establish latent infection in neurones, there are important differences in pathophysiology, as reviewed by Meier and Straus.[17] Unlike HSV, VZV may arrive at ganglia by the haematogenous route and cannot be cultured during latency. There is no response to sensory stimuli or asymptomatic shedding, and reactivation rarely occurs more than once. Cutaneous involvement after reactivation follows a dermatomal distribution.

One possible explanation for these differences is the site of latent infection.[17] Although HSV DNA is clearly located in neuronal nuclei, VZV is found in other (satellite) cells in sensory ganglia, with or without neuronal involvement. Reactivated VZV replicates throughout the ganglia, spreading to other non-neuronal and neuronal cells.

### 2.3 Herpes Zoster

Herpes zoster manifests clinically as a vesicular rash in a unilateral, dermatomal distribution, most commonly thoracic (T5-T12) or the ophthalmic branch of the trigeminal nerve.[3,16] Onset of the rash may follow a short prodromal illness and typically lasts 3–7 days before crusting, and then heals over several weeks. In immunosuppressed patients, such as those with an HIV infection or following bone-marrow transplantation, more than one dermatome may be involved and disseminated infection may result, with widespread cutaneous and visceral involvement.[16]

In acute zoster there is histological evidence of partial skin denervation, with neuronal loss in the dorsal root ganglion.[4] Loss of neurites in the epidermis may also occur to a lesser degree on the contralateral side.[18] The whole neuraxis is involved, with mononuclear cell infiltration and haemorrhagic necrosis of the dorsal root ganglia, nerve root and peripheral nerve. There may be evidence of spinal cord dorsal horn degeneration, unilateral segmental myelitis and leptomeningitis, sometimes involving adjacent spinal cord levels. Autopsy studies have found relative atrophy of the dorsal horn in patients who have had zoster compared with those who have not.[19]

### 2.4 PHN

The pain of both acute zoster and PHN is neuropathic in origin and may be constant and burning in character, or transient and lancinating. During the prodromal period pain may be caused by inflammation of the nerve sheath.[20] Pain during acute zoster can reflect inflammation of the sensory ganglia, skin, peripheral nerves and dorsal horn of the spinal cord.

Sensation can be significantly altered in patients with acute herpes zoster and these changes may persist after resolution of skin rash. The central affected area typically has decreased sensation (hy-

poaesthesia), surrounded by areas with abnormal, unpleasant sensations (dysaesthesia), including tingling. Allodynia, the perception of pain in response to non-painful stimuli, can occur in response to either mechanical or thermal stimulation.[4]

The mechanisms of PHN and allodynia are probably multiple and are incompletely understood. An excellent review outlines the current hypotheses for various mechanisms.[21] The different types of pain probably result from varying degrees of neuronal injury following zoster, with subsequent abnormal nerve impulses and/or connections.

Following injury, regenerating and sprouting peripheral nerve axons may discharge spontaneously, causing the typically constant aching or burning pain.[20] Similar spontaneous discharges may occur in the proximal part of the nerve, near the dorsal root ganglion.[21] A second possible mechanism to explain spontaneous pain is 'central sensitisation', where spinal cord sensory neurones become hyperexcitable because of chronic stimulation by C-fibre nociceptors from nearby healing areas.[22] A third mechanism is 'central disinhibition', where dorsal horn sensory neurones lose the usual inhibitory signals from Aβ-fibres and lower their threshold for firing.[21] In some patients, psychosocial aspects such as anxiety, depression, low life satisfaction and greater disease conviction may contribute to the development of chronic pain.[23,24]

The phenomenon of allodynia occurs when a non-painful input from peripheral nerves results in the central perception of pain and has been found in up to 87% of patients with PHN.[25] Fields et al. describe two main clinical patterns of allodynia and propose possible mechanisms for each.[21] Some patients have preserved sensation and their severe allodynia may be due to 'irritable nociceptors', which are anatomically intact but abnormally hyperactive primary afferent nociceptors. In contrast, patients with significant scarring may have extensive loss of nociceptive C-fibres and experience allodynia due to 'deafferentation'. Following degeneration of C-fibres in areas of scarring, abnormal connections may form between Aβ low-threshold mechanoreceptors and second-order pain transmission neurones in the spinal cord. This results in light cutaneous stimulation being perceived inappropriately as pain.[21] A similar mechanism has been proposed for other causes of neuropathic pain, including reflex sympathetic dystrophy.[20,26]

## 3. Potential Approaches for the Prevention of PHN

There are several possible approaches to preventing PHN based on its pathogenesis. By preventing primary infection, such as through vaccination, initial nerve damage and establishment of latent infection in sensory ganglia may be prevented. Early treatment of acute varicella infection with antiviral drugs may reduce the burden of latent viral infection or ideally prevent it altogether. Once latent infection is established, a specific treatment that could eradicate latent virus from sensory ganglia should, in theory, prevent reactivation and subsequent neuralgia. Unfortunately, no such treatment is currently available. Perhaps the most promising intervention is to stimulate waning specific anti-VZV immunity in the elderly or immunocompromised individuals by vaccination to prevent reactivation.

Once viral reactivation has occurred, therapy should be directed at minimising damage to the nervous system, thereby reducing the incidence and severity of PHN. Antiviral drugs given during active herpes zoster should limit the amount of viral replication and subsequent damage. Anti-inflammatory therapies, by reducing the host response to viral replication, should also limit damage to neurones. If drugs were available that influenced nerve healing by stimulating appropriate regrowth and limiting abnormal synapse formation, they may help reduce postherpetic allodynia and neuralgia.

Once PHN has become established, the role for antiviral and anti-inflammatory therapy is limited. Treatment is directed at decreasing abnormal neural signalling, or is used to simply control the symptoms of pain (analgesia). Chronic neuropathic pain is notoriously difficult to treat, and various other rehabilitation strategies such as behavioural or psychological therapies may be necessary to decrease disa-

**Table I.** Treatments to prevent postherpetic neuralgia (PHN)

| Treatment | Efficacy | Adverse effects |
|---|---|---|
| Aciclovir, valaciclovir, famciclovir | Shorten the duration of varicella. Accelerate recovery from zoster. Reduce the incidence of PHN | Reversible renal impairment (mainly IV aciclovir), neurotoxicity (rare) |
| Foscarnet | May be useful with aciclovir-resistant herpes simplex virus (thymidine kinase mutations) | Reversible renal impairment, neurotoxicity, rash, fever |
| Vidarabine | Inferior efficacy to aciclovir | Teratogenic effects, oncogenic effects, possible CNS toxicity |
| Corticosteroids | Improvement in acute symptoms; no reduction in PHN | Gastritis, hepatic disturbance, impaired glucose tolerance |
| Varicella vaccine | Prevents varicella (especially in children) but may not prevent zoster. May boost immunity in elderly. Heat-inactivated vaccine safe and efficacious for zoster prophylaxis in haematopoietic cell transplantation | Local reaction, occasional fever and rash |

**IV** = intravenous.

bility in the face of ongoing pain. Table I provides a summary of the treatments used to prevent PHN.

## 3.1 Antiviral Drugs

### *3.1.1 Aciclovir*

#### Pharmacology

Aciclovir was the first antiviral drug with good efficacy against herpes viruses, including VZV, and has been widely used.[27] It is a deoxyguanosine analogue (9-[2-hydroxyethoxymethyl]-9H-guanine), which is phosphorylated by a virus-encoded thymidine kinase (TK) to aciclovir monophosphate.[27] Further phosphorylation by cellular kinases results in the active aciclovir triphosphate, a competitive inhibitor of viral DNA polymerase and a DNA chain terminator. Its high therapeutic index is due to its preferential inhibition of viral, rather than cellular, DNA polymerase and its reliance on viral TK for activation. Viral resistance can emerge in VZV and HSV because of mutation or poor expression of viral TK.

Aciclovir is approximately 10-fold less active against VZV than HSV-1 and -2, with an *in vitro* inhibitory concentration of 0.8–4.0 μg/mL.[27] Aciclovir is widely distributed in body fluids and has a mean plasma elimination half-life of 2.5–3 hours in patients with normal renal function. Oral bioavailability is low (15–21%), with peak plasma concentrations ranging from 0.4 μg/mL after a 200mg dose to 1.6 μg after an 800mg dose.[27]

Aciclovir is extremely well tolerated, with the most common serious adverse effects being reversible renal impairment and neurotoxicity.[28] Renal impairment occurs in approximately 5% of patients receiving intravenous aciclovir, as a result of crystalline nephropathy or interstitial nephritis.[27] Neurotoxicity occurs rarely in the absence of renal dysfunction, affecting 1–4% of patients overall and causing lethargy, confusion, tremor, obtundation and other rarer effects.[27] Local irritation can follow intravenous injection of aciclovir, and oral aciclovir infrequently causes gastrointestinal adverse effects and headaches.[27]

#### Clinical Trials

Aciclovir treatment of primary varicella has been studied in children and adults in randomised, placebo-controlled trials.[29-31] Oral aciclovir, given within 24 hours of rash onset, led to more rapid clinical improvement but no change in the overall rate of complications. There were insufficient data to comment on subsequent rates of herpes zoster. Aciclovir was well tolerated with no detectable change in renal function, one case of transient nausea and a case of urticaria.[31]

There have been two trials of intravenous (IV) aciclovir for acute zoster in immunocompetent patients.[32,33] These trials showed a reduced duration of skin lesions, viral shedding and acute pain, but no significant reduction in PHN. IV aciclovir was well tolerated overall, with no adverse effects in one group of patients with a mean age of 67 years[32] and

a transient rise in creatinine in the other group (mean age 52 years), associated with nausea.[33]

Two further trials provide data on aciclovir toxicity in immunocompromised patients. In patients with herpes zoster following bone marrow transplantation, 3 of 11 patients receiving IV aciclovir (500 mg/m$^2$ three times daily) had elevated serum creatinine, although all three were also taking cyclosporine at the time.[34] In 37 patients receiving IV aciclovir for disseminated zoster, one patient became disoriented, although the cause was unclear.[35]

There have been several trials of oral aciclovir for the treatment of acute zoster. The dose has ranged from 400[36-38] to 800mg,[38-41] five times a day for 5–10 days. Oral aciclovir was well tolerated in all of these trials. Gastrointestinal adverse effects,[38] headaches, depression, nausea, vomiting and fatigue[39] were reported in some trials, but more commonly in the placebo than the aciclovir groups. There was no disturbance of renal function, hepatic function or blood count with oral aciclovir in any of these studies.

Oral aciclovir reduced time of viral shedding,[38] time to healing of rash,[38-40] frequency of dissemination[39,40] and time to resolution of acute pain.[38-40] In a comparison between oral and IV aciclovir, no difference in efficacy was found.[36]

The effect of aciclovir on PHN was less consistent, partly because of varying definitions between the trials. If the duration of 'zoster-associated pain' is considered as a continuum, a reduction in the mean duration of pain can be demonstrated.[42,43] However, since most patients have acute but not prolonged pain, reducing the duration of acute pain can have a large effect on the median duration of pain using this method.[8] Thus, the decreased median duration of zoster-associated pain does not necessarily reflect a reduction in true PHN.

A meta-analysis of the four randomised, placebo-controlled trials of oral aciclovir in herpes zoster included a total of 691 patients.[44] It confirmed the benefits of aciclovir on acute pain and the overall duration of zoster-associated pain. In addition, it demonstrated at least a 50% reduction in PHN at 3 and 6 months with aciclovir treatment, with greater benefits for patients aged ≥50 years.

#### 3.1.2 Valaciclovir

##### Pharmacology

Valaciclovir is the L-valyl ester prodrug of aciclovir. It is well absorbed orally and is rapidly converted to aciclovir by intestinal and hepatic valaciclovir hydrolase.[27] Overall bioavailability is 54% and total aciclovir exposure (area under the curve) is similar to intravenous aciclovir, with peak plasma aciclovir levels of 5.0 and 8.5 μg/mL after valaciclovir doses of 1000 and 2000mg, respectively. Elimination and viral resistance are the same as for aciclovir.

##### Clinical Trials

Compared with aciclovir, valaciclovir has a superior pharmacokinetic profile,[45] therefore, valaciclovir should be at least as efficacious as oral aciclovir, but potentially more toxic. A randomised trial, involving 1140 patients aged >50 years, compared valaciclovir with oral aciclovir.[46] Valaciclovir shortened the duration of zoster-associated pain and decreased the incidence of PHN at 6 months from 25.7% to 19.3%. There was no difference between the groups in rash healing, pain intensity or quality of life and no advantage of 14 days of treatment over 7 days. Adverse events related to treatment were similar in both groups and mostly mild. Over 10% of patients in each group reported mild nausea or headache. Only one severe adverse reaction was possibly attributed to valaciclovir: a severe headache in a 14-day valaciclovir recipient.

#### 3.1.3 Famciclovir

##### Pharmacology

Famciclovir is the diacetyl ester of 6-deoxy penciclovir, an acyclic guanosine analogue.[27] Famciclovir is well absorbed orally and rapidly converted to penciclovir by deacetylation and oxidation in the intestinal wall and liver. The overall bioavailability is 77%, with peak penciclovir plasma levels up to 4.0 μg/mL after a single 500mg dose of famciclovir.[47]

Penciclovir triphosphate is a competitive inhibitor of viral DNA polymerase but is not an obligate chain terminator. Although less active than aciclovir, penciclovir has much higher intracellular concentrations and half-life. Penciclovir is dependent on viral TK for activation, so is inactive against TK-deficient virus.[48]

Clinical Trials

Famciclovir has been shown to accelerate lesion healing, reduce duration of viral shedding and reduce the duration of zoster-associated pain by 2.6 times in patients aged >50 years, compared with placebo, with no significant difference in adverse effects.[49]

In a direct comparison between famciclovir and valaciclovir, there was no significant difference in the resolution of zoster-associated pain and no difference in residual pain after 1, 3 or 6 months.[50] Adverse events were reported in 34% of valaciclovir and 38% of famciclovir recipients, most commonly mild headaches or gastrointestinal disturbances such as nausea, constipation and diarrhoea. There were no significant changes in haematological or biochemical profiles and the few serious adverse events were believed to be unrelated to the study drugs.

#### 3.1.4 Foscarnet

Pharmacology

Foscarnet (trisodium phosphonoformate) is an inorganic pyrophosphate analogue that directly inhibits viral DNA polymerase and maintains activity against viruses with TK deficiency or mutation.[27] Its main adverse effects are reversible nephrotoxicity and electrolyte disturbances (33% patients); CNS adverse effects including tremor, irritability, seizures and hallucinosis (25%); and, rarely, fever, rash, gastrointestinal adverse effects, abnormal liver function tests and general fatigue.[27]

Clinical Trials

Foscarnet has been effective in some HIV-positive patients with aciclovir-resistant VZV or HSV.[51,52] In one series, detailing 26 courses of foscarnet, the most common adverse effects were hyperphosphataemia (19%), nausea and/or vomiting (15%), renal impairment (15%), proteinuria (15%), neutropaenia (12%) and hypocalcaemia (12%).[52] In this series, foscarnet therapy was discontinued in three patients as a result of adverse effects: one because of worsening renal impairment; and two because of neutropaenia.

#### 3.1.5 Vidarabine

Pharmacology

Vidarabine (9-β-D-ribofuranosyladenine) is an adenosine analogue that competitively inhibits viral and cellular DNA polymerase and acts as a DNA chain terminator.[27] It is phosphorylated by cellular enzymes to its active triphosphate and so retains activity against TK-deficient or -defective virus. Vidarabine is potentially mutagenic, teratogenic and oncogenic, as well as causing local ocular irritation. Its use is now restricted to topical treatment of kerato-conjunctivitis, mostly due to HSV.

Clinical Trials

There have been two major trials comparing IV vidarabine with IV aciclovir for zoster in immunocompromised patients.[34,35] In both trials, vidarabine was less efficacious than aciclovir for acute endpoints, with no difference in the incidence of PHN. There was no evidence of nephrotoxicity due to vidarabine, but several episodes of possible neurotoxicity with tremors, confusion and seizures. Although vidarabine is no longer recommended in this setting, it may have future application for serious infections with aciclovir-resistant virus.

### 3.2 Corticosteroids

The use of corticosteroids has been proposed to reduce the inflammation of peripheral nerves and sensory ganglia in herpes zoster, thereby limiting neuronal damage, scarring and the development of PHN.

There have been two randomised, placebo-controlled trials to examine the efficacy of corticosteroids in PHN.[53,54] In one study, the addition of prednisolone to aciclovir led to the faster resolution of acute pain and improved rash healing, but no difference between aciclovir alone and aciclovir plus prednisolone was seen at 6 months.[53] Of the 400 patients enrolled in the study, 64 (16%) exper-

ienced an adverse event: 38 (19%) in the group receiving aciclovir plus corticosteroid, compared with 26 (13%) in the group receiving aciclovir alone ($p > 0.1$). Of these adverse events, more in the corticosteroid plus aciclovir group were attributed to the study medication than in the aciclovir alone group (31 vs 13 events). The most common adverse events were dyspepsia, which was more common in patients receiving corticosteroid (9 vs 1 event) and transient increases in haemoglobin, neutrophil and platelet counts or in serum urea (6 vs 5 events). Three serious adverse events were observed: a case of haematemesis that was attributed to prednisone treatment, a chest infection and a case of bronchopneumonia.[53] In the second trial, prednisone with or without aciclovir reduced pain acutely, aciclovir with or without prednisone accelerated rash healing and the combination of aciclovir and prednisone accelerated vesicle crusting compared with placebo.[54] Both aciclovir and prednisone independently improved quality-of-life measures, but there was no significant effect of either drug on the resolution of zoster-associated pain or the development of PHN. Overall, 21% of patients experienced at least one adverse event: 22% in the aciclovir plus prednisone group, 27% in the aciclovir plus prednisone placebo group, 24% in the prednisone plus aciclovir placebo group and 12% in the double placebo group. These differences were not statistically significant. The most common adverse events were nausea or vomiting, which occurred in approximately 21% of patients overall. Other adverse events, reported in <2% of all patients, included oedema, increased leukocyte counts and altered platelet counts, bilirubin levels or liver function tests.[54]

## 3.3 VZV Vaccine

### 3.3.1 Primary Prevention of Varicella

Vaccination against varicella aims to prevent the establishment of latent VZV infection in sensory ganglia and subsequent zoster. The current live attenuated VZV vaccine is based on the 'Oka' strain.[55]

VZV vaccine stimulates effective humoral and cell-mediated immunity in children, with an efficacy between 88% and 95%, although a second dose is recommended in adolescents and adults.[56,57] It is well tolerated in children and adults, with fever and rash reported in 4% of patients.[57,58]

Naturally-acquired varicella in VZV vaccine recipients, although mild or subclinical, can cause latent infection. The Oka strain can itself establish latent infection and cause zoster, although at a lower rate than wild-type varicella.[58-60]

### 3.3.2 Secondary Prevention of Herpes Zoster

The use of VZV vaccine in older adults has been proposed to stimulate specific cell-mediated immunity and reduce the incidence of herpes zoster.[61] In one study, 202 adults aged >55 years (mean age 65.8 years) were given VZV vaccine and their immune markers were monitored for 4 years.[62] The vaccine was well tolerated, with local reactions in <25% of recipients and significant fever in <1%. An initial rise in VZV antibody persisted for 1 year, although the increase in VZV-specific cell-mediated immunity persisted longer, with a mean half-life of 54 months.[62] During 800 patient-years of follow-up there were eight probable episodes of herpes zoster, three of which were confirmed. None of the episodes were clinically severe and none of the patients developed PHN.

To resolve whether VZV vaccination in adults can reduce the incidence or severity of herpes zoster in the elderly population, a large prospective, placebo-controlled, randomised trial following 27 000 individuals over at least 3 years is required.[61]

Heat-killed Oka vaccine was recently trialled in patients receiving autologous haematopoietic-cell transplants for non-Hodgkin's or Hodgkin's lymphoma, in whom live vaccine is contraindicated.[63] The vaccine was given within 30 days before the transplant, then at 30, 60 and 90 days afterwards. There were no serious adverse effects and a significantly lower rate of zoster in vaccinated patients correlated with the reconstitution of VZV-specific CD4 T-cell immunity.

**Table II.** Treatment of established postherpetic neuralgia (PHN)

| Treatment | Efficacy | Adverse effects |
|---|---|---|
| Amitriptyline, nortriptyline, desipramine, maprotiline | May relieve neuropathic pain (more with norepinephrine than serotonin reuptake inhibitors) | Blurred vision, dry mouth, urine retention, constipation, sedation, exacerbation of glaucoma, aggression |
| Gabapentin | Reduced pain and sleep problems | Drowsiness, dizziness, ataxia, peripheral oedema, infection |
| 5% Lidocaine patch | Relief of allodynia | Local irritation |
| Capsaicin (topical) | Reduced neuropathic pain | Burning sensation, irritation |
| Lidocaine (IV) | Reduced pain severity | Nausea, light-headedness, circumoral paraesthesia, confusion |
| Oxycodone morphine | Reduced pain, relief of allodynia | Nausea, constipation, delerium, dose tolerance |
| Ketamine | Useful in comparative trials for spontaneous pain, relief of allodynia | Pruritus, painful induration, psychodysleptic and cognitive effects |
| Intrathecal methyl prednisolone | Reduced pain, diclofenac requirements with intractable PHN | Long-term complications (e.g. arachnoiditis) not excluded |
| Aspirin in ether or chloroform | Not proven | Flammable, toxic if inhaled, safe disposal difficult |
| Vincristine by iontophoresis | Not proven | Potential cytotoxicity, peripheral neuropathy |
| Surgery, nerve blocks | Anecdotal benefit in some patients with intractable pain | Potential nerve injury and complications of surgery |

**IV** = intravenous.

## 4. Potential Approaches for the Treatment of PHN

A management strategy should be developed following thorough assessment of all aspects of the condition including psychosocial status, neurological changes and concomitant disease processes and treatment. A study of zoster pain on activities of daily living suggested pain rated as ≥3 on a 0–10 numerical scale was significant.[64] A pain reduction of two points on this scale indicates clinically significant improvement.[65]

Following evaluation and careful explanation of PHN to the patient with general advice regarding activity levels, social interaction, use of natural fibre clothing and ice packs, evidence suggests that initial therapy should normally be with a tricyclic antidepressant drug (amitriptyline, nortriptyline, desipramine) or gabapentin.[66] It may be extrapolated from existing studies that both drugs are more or less equally efficacious.[67] Tricyclic antidepressants have more adverse effects and are more likely to interact with other drugs and disease processes. Gabapentin is more expensive but better tolerated with a higher safety profile.[68]

It is important to provide clear verbal explanations and instructions for the patient and carers and to contact the patient frequently to check compliance, monitor and advise regarding adverse effects and adjust therapy. Many apparent 'failures' with amitriptyline are because of non-compliance or unacceptable adverse effects following a single, often inappropriately large, dose.

Many treatments are proposed in the literature, often without supporting evidence of efficacy. Chekhov noted in *The Cherry Orchard* that where many treatments are available for a disease, it is because none of them work.[69] Where PHN is concerned, the situation is improving although in many patients pain persists despite appropriate management. Table II provides a summary of PHN treatment options.

### 4.1 Tricyclic Antidepressants

Amitriptyline, nortriptyline, desipramine and maprotiline have all been used with some benefit in PHN.[70-75] All may relieve neuropathic pain independent of the presence of depression. Drugs affecting norepinephrine reuptake are more effective than those affecting serotonin reuptake. All have anticholinergic adverse effects; however, desipramine is

less sedating than other tricyclic antidepressants, and nortriptyline seems slightly more acceptable to patients than amitriptyline.[76]

Analgesia probably results from both central and peripheral actions. Patients need to be aware of potential adverse effects such as drowsiness, dry mouth, constipation and increased appetite[77] and be taught the means of coping with these, for example with a high-fibre diet, artificial saliva spray or lozenges. Blurred vision, urinary retention and exacerbated glaucoma may rarely occur, as may a change of mood with aggression.[77] It is preferable to prescribe tricyclic antidepressants for once daily use about 1.5 hours before bedtime. A starting dose of 25mg is appropriate in the younger adult, elevating in increments of 25mg at weekly intervals, adverse effects permitting, until a beneficial effect is achieved or a maximum dose of approximately 100–125mg is reached. In the elderly and frail a reduced starting dose (10mg) with weekly increments of 10mg should minimise adverse effects.[78]

The typical frequency of specific adverse events associated with tricyclic antidepressants in patients with PHN include: dry mouth in up to 100% of patients (30% intolerable), constipation in 40–50% (5% intolerable), drowsiness in 15–20% (5% intolerable) and dizziness, tremor, nausea, lethargy or urinary retention, each occurring in around 5% of patients.[75]

If one tricyclic antidepressant drug does not produce benefits, it may be appropriate to try an alternative.

## 4.2 Anticonvulsants

### *4.2.1 Gabapentin*

Gabapentin was the first anticonvulsant with proven benefit in PHN.[79] A randomised, double-blind study comparing gabapentin (up to 3600mg daily) with placebo in 229 patients with PHN showed reduced pain and sleep interference, with improved mood and quality of life.[79] Minor adverse events were reported more commonly in patients receiving gabapentin (54.9%) than placebo (27.6%). The most frequently reported adverse events among the gabapentin group, which occurred at higher rates than in the placebo group, were somnolence (27.4% vs 5.2%), dizziness (23.9% vs 5.2%), ataxia (7.1% vs 0.0%), peripheral oedema (9.7% vs 3.4%) and infection (8.0% vs 2.6%).[79] There were no serious adverse events attributed to gabapentin.[79] A similar proportion of patients withdrew from the gabapentin (13.3%) and placebo (9.5%) groups as a result of adverse events attributed by the patient to the study medication.[79] Confirmation of the beneficial effects of gabapentin has been published by Rice and Maton.[80] Gabapentin should be used with caution in patients with myasthenia gravis, as it has been reported to occasionally exacerbate weakness.[81]

Achieving compliance requires careful discussion with the patient of expected benefits and adverse effects, the rate of dose elevation and the target dose. Dose elevation should be slower in the elderly to reduce the risk of adverse events; the maximum dose may need to be reduced in patients with impaired renal function. Once satisfactory analgesia has been attained the patient may continue taking a stable dose for about 2 months before careful titration downward to establish the minimum effective dose.

Few studies of older anticonvulsants, phenytoin, carbamazepine or sodium valproate would justify inclusion in contemporary meta-analyses. It would appear that carbamazepine is of little benefit in PHN and may cause serious confusion and sedation in some elderly people. Lamotrigine, vigabatrin and topiramate may all have some beneficial effect, although the dermatological complications of lamotrigine may be more common and more severe. Pregabalin, at a dosage of 150 or 300 mg/day, was beneficial in a recent randomised, placebo-controlled trial.[82] The most frequent adverse effects, mild to moderate in intensity, were dizziness, somnolence, headache and dry mouth, as well as some dose-dependent peripheral oedema and weight gain. The benefit-to-adverse effect ratio is an important factor in planning therapy and can be calculated by dividing the absolute risk reduction for benefit by the absolute risk reduction for harm. For instance, if the benefit-to-adverse effect ratio for a given drug is

5, that would mean that for every five patients who obtain a benefit from the drug, one would suffer an adverse event.[67] The benefit-to-adverse effect ratio has been calculated as 6 for gabapentin, compared with 4 for tricyclic antidepressants.[67]

## 4.3 Topical Drugs

### 4.3.1 Lidocaine 5% Patch

Where allodynia (pain in response to the application of a normally non-noxious stimulus such as light brushing or a cool breeze) is a significant component of PHN, topical application of local anaesthetic may be valuable. Creams and gels are messy and difficult to control. A preparation of 5% lidocaine absorbed into a self-adhesive patch (Lidoderm®)[1], which may be cut to the size and shape of the affected area, is available. Published trials and personal experience suggest a high level of patient satisfaction.[83-86] Adverse effects seem to be limited to local irritation and this may be minimised by a gradual increase in the time for which the patch is worn in the first few days or weeks.[83-86]

### 4.3.2 Capsaicin

Capsaicin (N-vanillyl-8-methyl-6-(E)-noneamide) is a pungent derivative of hot chilli peppers. The application of capsaicin to sensory nerve tissue first stimulates then inhibits (by causing depletion of the neurotransmitter substance P) activity in nociceptive C-fibres. A 0.075% preparation of capsaicin has been reported to provide a significant benefit in the treatment of PHN.[87-89] Placebo blinding is difficult in controlled studies of capsaicin because of the burning sensation associated with the active treatment.

## 4.4 Opioids

It is now known that, contrary to older beliefs, opioids may be effective in controlling neuropathic pain. Oxycodone reduces pain and allodynia compared with placebo.[90] Morphine (IV) has been shown to reduce pain intensity of PHN in one randomised, double-blind, placebo-controlled trial.[91] Sustained-release tramadol[92] and levorphanol[93] were also beneficial in recent randomised trials. There is anecdotal evidence that methadone is effective, although dihydrocodeine may also be considered.[94]

The major adverse effects of opioids are nausea, constipation, delirium, with most problems in the frail and elderly.[95] Some patients also have increasing dose requirements because of the phenomenon of opioid tolerance.[95] One of the most worrying adverse effects of opioid therapy is opioid dependence, which results in psychological craving, as well as a characteristic withdrawal syndrome if the drug is ceased abruptly. The opioid withdrawal syndrome is characterised by rhinorrhoea, lacrimation, yawning, chills, goose pimples, hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhoea, anxiety and hostility.[95] Despite these concerns, dependence and withdrawal have not been significant issues in trials of opiates for patients with PHN.[94,96]

## 4.5 NMDA Antagonists

### 4.5.1 Ketamine

There have been no controlled trials of the NMDA receptor antagonist ketamine in PHN but evidence that it may be effective for reducing pain comes from a non-comparative trial in five patients.[97] A continuous subcutaneous infusion of ketamine was effective in relieving the spontaneous pain and allodynia of PHN. However, itching and painful induration at the injection site were common and other adverse effects included nausea, fatigue and dizziness. Other recognised adverse effects of ketamine include psychodysleptic and cognitive effects, which can be particularly problematic for elderly patients. Several of these adverse effects were observed during a successful trial of ketamine in patients with cold allodynia, but only a few patients reported them to be disturbing.[98]

Another NMDA antagonist, dextromethorphan (mean dosage 439 mg/day), did not reduce pain in 13 patients with established PHN when compared

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

with placebo, although it was effective in diabetic neuropathy in the same trial.[99]

### 4.6 Systemic Local Anaesthetics

There have been many studies where local anaesthetic agents, especially lidocaine, have been given systemically to treat PHN. A recent systematic review has confirmed the efficacy of these agents for non-cancer-related neuropathic pain, including PHN.[96] IV lidocaine was the most widely studied drug and was generally well tolerated at a dose of 5 mg/kg infused over 30 minutes.[96] Reported adverse events include mild nausea (37%) and light-headedness (5%) in patients with PHN;[97] nausea and perioral numbness (20%) or drowsiness, dysarthria and tremor (10%) in patients with fibromyalgia;[100] and somnolence, nausea, circumoral paraesthesia, euphoria or confusion in up to 40% of patients receiving IV lidocaine for metastatic cancer pain.[101]

Mexiletine can be administered orally and has been used in at least three studies of neuropathic pain, at doses ranging from 225 to 750mg.[96,102-104] It has been shown to be effective for pain as a result of peripheral nerve damage but has never been studied specifically in PHN. Mild dose-related adverse effects include nausea,[102,103] hiccups and tremor.[103]

### 4.7 Nerve Blocks, Intrathecal Drugs and Surgery

In extreme cases of PHN refractory to other measures, patients and physicians have resorted to surgery and there is anecdotal evidence for skin excision, sympathectomy, dorsal root entry zone lesions, cordotomy, thalamotomy, cingulumotomy and spinal cord and deep brain stimulation.[105] The potential for severe complications must be carefully considered and explained. The potential for severe complications such as bleeding, infection and neurological damage must be carefully considered and explained. Targeted electrocoagulation of the dorsal root in PHN has resulted in prolonged hemiparesis and sensory deficits[4,106] and is no longer recommended in a recent consensus statement.[107]

A highly controversial paper from Kotani and colleagues reported the use of intrathecal methyl prednisolone in patients with long-standing PHN that had been resistant to conventional therapy.[108] Weekly methyl prednisolone (60mg) plus lidocaine for 4 weeks was superior to lidocaine alone or placebo in alleviating pain and reducing diclofenac consumption.[108] Serious adverse events were not evident up to 2 years after treatment.[108] However, arachnoiditis has been reported previously in patients receiving this treatment for multiple sclerosis and there is concern that adverse effects on the meninges and spinal cord may develop as a very delayed complication.[109]

### 4.8 Unproven Treatments

There have been several studies of topical aspirin suspended in ether, chloroform or acetone.[110-114] Although the authors claim a benefit, the trials were of short duration and safety was a concern (flammability, inhalation risk, safe disposal).

Anecdotal reports of pain relief using iontophoresed vincristine were not supported by subsequent controlled trials of this toxic therapy.[115]

Many alternative therapies have been suggested for use in PHN, including homeopathy, acupuncture, transcutaneous electrical nerve stimulation (TENS), topical benzydamine, geranium or peppermint oil, cryotherapy and many others. There is no scientific evidence to support the use of these treatments and they cannot be recommended.

Multidisciplinary pain management programmes exist for people experiencing pain not controlled by conventional or complementary therapies. Research into the effectiveness of such programmes for patients with intractable PHN is needed.

### 4.9 Guidelines

A number of guidelines for zoster and PHN management exist but earlier ones do not conform to contemporary requirements for such documents. The International Herpes Management Forum (IHMF) is completing the peer review process of such a guideline and this is available on their website.[116] Older guidelines include those of the IHMF

and British Society for the Study of Infection (BSSI).[117,118] Certainly guidelines should adhere to contemporary evidence-based standards.[119]

## 5. Conclusions

There are many approaches to preventing or treating PHN, each with differing efficacy and tolerability. Primary prevention of varicella using widespread VZV vaccination is potentially the most effective approach and is well tolerated overall. VZV vaccination in older adults is well tolerated and has been shown to boost VZV-specific cell-mediated immunity but awaits further large trials to assess efficacy in preventing herpes zoster. Treatment of acute varicella with aciclovir is well tolerated and shortens the duration of illness, especially in adults. Any long-term benefits on the incidence of herpes zoster are unknown.

In patients with herpes zoster, prompt treatment with aciclovir, valaciclovir or famciclovir (within 72 hours of rash) accelerates recovery, reduces the median duration of zoster-associated pain and may reduce the incidence of PHN. In immunosuppressed patients with disseminated zoster, intravenous aciclovir should be given, while monitoring renal function. All three oral drugs are well tolerated and aciclovir is the most studied of the three. However, valaciclovir and probably famciclovir are more efficacious than aciclovir and achieve more therapeutic plasma drug levels with less frequent, more convenient administration because of their superior pharmacokinetic profiles. There is no compelling evidence to recommend valaciclovir or famciclovir over the other, with the one published comparative trial showing equivalent efficacy and safety.[50]

In older patients with severe zoster and significant acute pain, a short course of prednisolone (if not contraindicated) can reduce acute pain, hasten recovery and improve quality of life, but does not reduce the incidence of PHN. In immunosuppressed patients with aciclovir-resistant zoster, foscarnet is the best alternative treatment, but clinical data are limited and drug toxicity is more significant than with aciclovir.

In established PHN, tricyclic antidepressants such as nortriptyline or the anticonvulsant gabapentin are the most proven treatments. There is some evidence that starting amitriptyline immediately in high-risk patients may reduce the incidence of PHN, but this requires further confirmation.[120] Opioids such as oxycodone or morphine may be helpful in some patients and NMDA receptor antagonists such as ketamine may have an increasing role in the future.[121] A trial of IV lidocaine may be warranted for persisting pain and if effective ongoing oral mexiletine could be considered.

Patient education is important to maximise treatment benefit and minimise adverse effects; in patients with chronic pain behavioural intervention and a multidisciplinary, holistic approach may be of benefit.

Topical treatment with 5% lidocaine patch or capsaicin is beneficial in some patients and are well tolerated overall. In severe, intractable cases intrathecal methyl prednisolone or surgery may be considered, but the safety of these interventions has not been established.

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