Postherpetic neuralgia
an update on management and prevention

An expanded range of treatment options has increased the likelihood of effective treatment of postherpetic neuralgia in individual patients but prevention remains the best treatment.

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Postherpetic neuralgia is the most common complication of herpes zoster, is often difficult to control and may lead to significant patient distress and depression. As postherpetic neuralgia is a disease predominantly of older people, it is appropriate to review this important topic following the 'Global Year against Pain in the Older Person' (see www.iasp-pain.org).

Herpes zoster (shingles) is a viral infection of sensory nerve cells caused by the same virus that causes varicella (chickenpox) and occurs following reactivation of a latent infection of this virus. The name of the virus – varicella zoster virus – reflects the nature of the two conditions it causes, initially varicella and later herpes zoster.

Herpes zoster is a common disease, developing in up to 20% of all people,[1] and is associated with significant morbidity, particularly in the elderly and/or immunocompromised patients. Complications in immunocompromised patients include encephalitis, myelitis, and cranial and peripheral nerve palsies. Pain is a prominent feature of acute herpes zoster, and may become debilitating and persistent in 30% of cases, then being known as postherpetic neuralgia.[2]

Clinical presentation

Herpes zoster can usually be diagnosed clinically by the typical appearance of a vesicular rash in a dermatomal pattern (Figure 1). However, early zoster may resemble herpes simplex when the lower sacral dermatomes or trigeminal nerve are affected. In these situations viral swabs for immunofluorescence or culture may be required for definitive diagnosis.[3]

Determining when postherpetic neuralgia begins following an acute episode of herpes zoster can be difficult. In fact, there is currently no generally

IN SUMMARY

- **Postherpetic neuralgia is the most common complication of acute herpes zoster.**
- **Once developed, postherpetic neuralgia is often difficult to manage. Efforts to prevent it are therefore crucial. Postherpetic neuralgia may be avoided by prevention of varicella zoster virus infection by paediatric vaccination, by boosting T-cell mediated immunity to the virus by adult vaccination or by treatments at the time of an acute herpes zoster infection.**
- **Careful attention should be paid to the physical, psychological and social consequences of the disease.**
- **The drug management of postherpetic neuralgia may involve tricyclic antidepressants, anticonvulsants, opioids and topical agents.**

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agreed definition of postherpetic neuralgia. This is because the pain of acute herpes zoster and postherpetic neuralgia are similar, and pain usually resolves slowly following rash healing.[4] Pain may also precede the rash in herpes zoster by three days or more. For these reasons, some consider herpes zoster pain as a continuum (zoster-associated pain, or ZAP) from onset to resolution (Figure 2). Recommendations from herpes zoster antiviral trials have suggested postherpetic neuralgia be defined as clinically significant pain (i.e. moderate, or more than 3 on a scale of 1 to 10) persisting beyond three months.[1]

Patients commonly describe pain during the acute phase of herpes zoster as tender, sharp, stabbing, shooting and throbbing in nature. The more persistent pain of postherpetic neuralgia is similar but may also be burning in nature (Table 1).[5,6] Tenderness in the skin over the affected area (allodynia) occurs in most patients with zoster-associated pain, and is a very distressing feature of this pain. Severe tenderness may result in extreme difficulty wearing clothes (including underclothes) and undertaking basic self-care, including hair brushing.

Epidemiology

In the general community most zoster-associated pain resolves within the first three months following the acute infection. Even patients with persistent pain have a tendency towards spontaneous improvement. While epidemiological studies vary with respect to the absolute incidence of postherpetic neuralgia, all agree that the incidence increases with age. Postherpetic neuralgia is uncommon in patients with herpes zoster below the age of 50 years but can occur in up to 50% of cases in those aged over 60 years.[1] Reactivation of the varicella zoster virus tends to occur only once in a lifetime, with a second episode occurring in fewer than 5% of people.[7]

An ability to predict which patients are most likely to develop persistent pain may assist in targeting treatments. Research has therefore been performed to determine factors associated with the development of postherpetic neuralgia. Several factors have been suggested, including age, severity of acute zoster-associated pain, extent of rash, female gender and ophthalmic location. Unfortunately these factors have not been shown to be easily used in general practice to predict which patients are most at risk of developing postherpetic neuralgia. Only age over 50 years and pain rated as more than 5 on a scale of 1 to 10 independently predicted postherpetic neuralgia, but the specificity of these factors for postherpetic neuralgia was poor.[8]

PHOTOLIBRARY

Figure 1. Herpes zoster rash on the chest of an elderly man. This is a classic example of the rash, being clearly dermatomal and occurring in one of the most common distributions (thoracic).

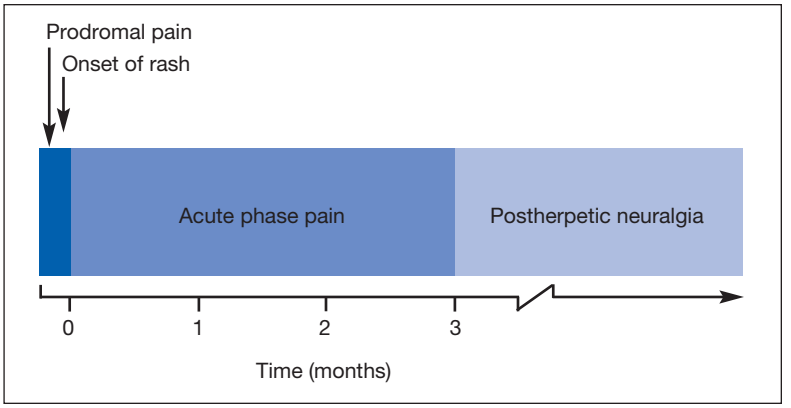

Figure 2. Zoster-associated pain.

Varicella zoster virus, ageing and immunity

The cause for varicella zoster virus reactivation remains unknown. In order for reactivation to

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Table 1. Types of pain in postherpetic neuralgia[6]

Constant background pain

- Fluctuates in intensity, often burning
- During recovery becomes absent for longer periods prior to diminishing in intensity

Paroxysmal pain

- Shooting pain through the area

Allodynia (painful hypersensitivity)

- Pain produced by light touch, particularly moving contact with skin
- Present in 90% of patients with postherpetic neuralgia
- Often very distressing
- Frequently last pain type to disappear

occur, the virus that has been latent in dorsal root ganglia must evade host immune responses as it divides and moves to the skin in the peripheral nerves arising in the affected root ganglia.

On initial exposure to varicella zoster virus, T-cell immunity develops to enable varicella resolution. Memory CD4 and CD8 T-cells able to identify varicella zoster virus proteins persist after the initial infection has resolved and maintain vigilance for viral recurrence.[9] This robust memory T-cell immunity is maintained by periodic boosting through community re-exposure to the virus or subclinical reactivation from latency, or by vaccination. Loss of varicella zoster virus-specific T-cell response increases an individual's susceptibility to herpes zoster, particularly when the person is immunocompromised (Figure 3, see the box on this page). Varicella zoster virus IgG antibodies persist despite declining T-cell immunity, and provide protection from recurrence of a more generalised infection (i.e. varicella).

Varicella zoster virus and immunity

Varicella is the primary infection caused by the varicella zoster virus, and its resolution is associated with the induction of varicella zoster virus-specific memory T-cells (VZVT-cells; blue line in the graph below). Memory immunity to varicella zoster virus may be boosted periodically by exposure to varicella or silent reactivation from latency (red peaks). Varicella zoster virus-specific memory T-cells decline with age. The decline below a threshold (dashed green line) correlates with an increased risk of zoster. The occurrence of zoster, in turn, is associated with an increase in varicella zoster virus-specific T-cells. The administration of zoster vaccine to older persons may prevent varicella zoster virus-specific T-cells from dropping below the threshold for zoster occurrence (dashed blue line).

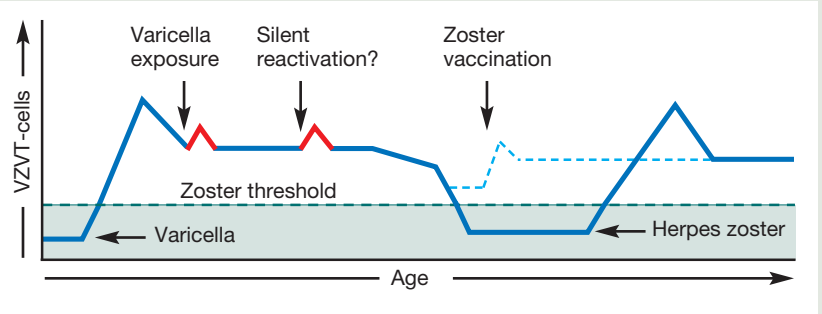

Figure 3. Host factors in varicella zoster virus latency and reactivation.

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Prevention of postherpetic neuralgia

Once developed, postherpetic neuralgia is often difficult to manage. Efforts to prevent its development are therefore crucial. It may be avoided by prevention of initial varicella zoster virus infection, prevention of varicella zoster virus reactivation (by boosting varicella zoster virus T-cell mediated immunity) or by treatments at the time of an acute herpes zoster infection (Table 2).[10,11]

A great deal of interest has been shown in the effect of vaccination to prevent the development of postherpetic neuralgia. Vaccination may be administered to prevent varicella zoster virus infection (paediatric immunisation [Varilrix, Varivax Refrigerated]) or to boost established immunity (adult vaccination [Zostavax]).[10]

Paediatric immunisation

The varicella zoster virus vaccine, a live attenuated vaccine, was initially developed to prevent varicella, the primary infection of the virus. However, as previously mentioned, varicella and zoster differ in the immune surveillance required to prevent their occurrences. Prevention of varicella is dependent on the presence of anti-varicella zoster virus IgG antibodies while herpes zoster is more dependent on T-cell mediated immune mechanisms.

Unfortunately, in adults, vaccines aimed at preventing varicella (Varilrix, Varivax Refrigerated; titre about 2000 plaque-forming units (PFU)/0.5 mL) do not reliably produce a durable increase in T-cell mediated immunity capable of preventing herpes zoster. In order to prevent herpes zoster (and therefore postherpetic neuralgia), a higher titre vaccine (Zostavax; titre, 19,400 PFU/0.65 mL) is required.[12]

Paediatric varicella vaccines should not be used in adults to prevent herpes zoster or postherpetic neuralgia. They can,

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Table 2. Prevention of postherpetic neuralgia

Prevent varicella zoster virus infection

- Paediatric varicella zoster virus vaccination at 18 months or 10 to 13 years[10]

Prevent varicella zoster virus reactivation

- Adult varicella zoster virus vaccination at 60 years of age and above

Acute herpes zoster management

- Antiviral treatment – reduces duration of acute zoster-associated pain but not postherpetic neuralgia
- Tricyclic antidepressant (low dose) may reduce postherpetic neuralgia[11]
- Standard pain management practices

however, be used in adolescents and adults to prevent varicella (two doses administered at least six weeks apart, compared to a single dose for infants and children up to and including 12 years of age.)

In Australia, varicella vaccination has been available since 1999. Since November 2005, vaccination has been funded in Australia (under the National Immunisation Program) for all non-immune children aged 18 months and 10 to 13 years.[13] There has been some controversy as to whether widespread paediatric immunisation will lead to a reduction in herpes zoster and postherpetic neuralgia. This is due to the inevitable waning of immunity over time and reduced exposure to circulating virus. These issues remain unresolved.

Adult immunisation

Based on a large randomised, double-blind placebo-controlled trial (the Shingles Prevention Study; n = 35,546 adults aged over 60 years), vaccination with a high titre live attenuated varicella zoster virus vaccine can reduce the incidence of both:[14,15]

- herpes zoster – by about 51%, number needed to treat [NNT] to prevent one case = 59, and
- postherpetic neuralgia – by about 66%, NNT to prevent one case of postherpetic neuralgia at six months with pain score above 2 on a scale of 1 to 10 = 802.

In patients who are severely immunocompromised (such as bone marrow transplant recipients), vaccination with a heat-inactivated live attenuated varicella zoster virus has also been shown to reduce the incidence of herpes zoster infection; protection was related to varicella zoster virus T-cell immunity.[16] (Heat-inactivation of a live attenuated virus has been used by some researchers to potentially improve the safety profile of the vaccine.)

The zoster vaccine Zostavax is registered in Australia for the prevention of herpes zoster, for the prevention of postherpetic neuralgia and for the reduction of acute and chronic zoster-associated pain in individuals aged 60 years and older. It has been available since about mid-2007. It is important to note that the TGA-approved indications do not include individuals who are immunocompromised or those in the 50 to 59 years age bracket.

Preventive measures during acute herpes zoster infection

Antiviral therapy

The benefit of antiviral therapy is limited to some degree because significant neurotoxic damage has often already occurred by the time the rash has appeared.[9] Antiviral therapy reduces the severity and duration of herpes zoster and acute zoster-associated pain but does not appear to reduce the incidence of postherpetic neuralgia.[14]

Antidepressant therapy

Commencing low-dose amitriptyline (Endep; 25 mg) within the first week of acute herpes zoster in patients with pain may reduce the incidence of postherpetic neuralgia. This is based on the results of a single randomised controlled trial (NNT to prevent one case = 5.1).[11,17]

Effective pain management

Provision of early and appropriate analgesia is an essential component of the management of herpes zoster. There is growing consensus that appropriate early treatment of pain may also result in a lower incidence of postherpetic neuralgia.[18]

Regional blockade

Regional blockade performed early in herpes zoster may promote healing of the acute rash and limit the development of postherpetic neuralgia. Sympathetic blockade is proposed to improve intraneural blood flow and when performed early in the disease may result in reduced neuronal destruction.[19] These observations have not, however, been adequately tested using well-designed trials.[20]

Management of established postherpetic neuralgia

Pain and distress may be influenced by a person's psychological, social and spiritual makeup. Careful assessment of these influences is needed before a broad treatment plan can be developed. In more complicated situations, contact with or referral to a pain medicine specialist may be warranted. Based on current evidence, a suggested approach to the pharmacological and nonpharmacological management of postherpetic neuralgia is given in Table 3.

Pharmacological therapies

Patients with postherpetic neuralgia are commonly recruited for research trials because their pain is well-defined. Despite this, the pharmacological management of postherpetic neuralgia remains ineffective in a significant proportion of patients. Why treatment is effective in some patients and ineffective in others remains unclear. Several possible reasons have been suggested, including differing underlying mechanisms despite similar

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Table 3. Postherpetic neuralgia management: a pragmatic approach using the best available evidence

	Constant or paroxysmal pain	Allodynia (hypersensitivity)	All postherpetic neuralgia pain
First-line therapy	• Tricyclic antidepressants (i.e. amitriptyline, nortriptyline) • Gabinoids (i.e. gabapentin, pregabalin) or sodium valproate • Opioids (i.e. oxycodone, morphine, methadone*)	• Firm garment (to reduce light brushing)	• Set realistic expectations regarding the likely effects of treatment • Consider need for increased social support (i.e. self care, domestic support) • Monitor: – affect/mood – behaviours (e.g. excess rest/social withdrawal) – cognitions/thoughts (e.g. that pain is a sign of ongoing damage)
Second-line therapy	• Tramadol • Oral corticosteroids	• Topical capsaicin • Physical desensitisation (program to gradually increase touch) • Topical 5% lignocaine patches†	
Any time	Specialist pain team involvement		

* Special caution is needed with methadone given its prolonged clearance. † Lignocaine patches require individual approval from the Therapeutics Goods Association using the Special Access Scheme (SAS).

initiating events, treatment dropout due to side effects and genetic variation in pain susceptibility.

Several pharmacological treatments have evidence to support their use in the management of postherpetic neuralgia (Table 4), but unfortunately most of the studies undertaken are short in duration (less than two months).[21,22] All medications initiated for the management of postherpetic neuralgia need to be reviewed regularly and reduced as the natural resolution of pain occurs.

Tricyclic antidepressants

The efficacy of the tricyclic antidepressants (TCAs) amitriptyline and nortriptyline (Allegron) in postherpetic neuralgia is well established (doses used are usually below 100 mg/day).[22] TCAs should be used with caution in elderly patients, particularly those with cardiac risks.

SSRIs and NSRIs

No randomised controlled trials assessing the efficacy of selective serotonin reuptake inhibitors (SSRIs) or noradrenaline serotonin reuptake inhibitors (NSRIs; e.g. venlafaxine) in postherpetic neuralgia are available. SSRIs do not appear to be effective analgesic agents in other neuropathic pain states.[22]

Gabinoids and sodium valproate

Several anticonvulsants have been shown to be effective in postherpetic neuralgia. These include gabapentin (at a dose of 1800 to 3600 mg/day),[23,24] pregabalin (Lyrica; at a dose of 150 to 600 mg/day)[25,26] and sodium valproate (Epilim, Valpro; at a dose of 1000 mg/day).[27] In a comparison between gabapentin and nortriptyline, similar efficacy was demonstrated for pain relief; however, gabapentin was better tolerated.[28] Recently, the use of valproate has reduced in comparison to the gabinoids (gabapentin, pregabalin) due to its less favourable side-effect profile.

In Australia, the gabinoids are not subsidised by the government, making their supply very expensive.

Opioids

Opioids such as morphine, methadone (Physeptone) and oxycodone (Endone, OxyContin, OxyNorm, Proladone) have been shown to result in a clinically significant reduction in postherpetic neuralgia pain intensity.[29,30] Of interest, a randomised controlled trial comparing opioids (methadone and morphine) and TCAs (nortriptyline and desipramine) found both drug groups were effective in postherpetic neuralgia but noted different populations responded to each group.[30] This observation supports the proposal that differing pain mechanisms exist in postherpetic neuralgia.

The mixed opioid, serotonergic and noradrenergic effects of tramadol (Tramahexal, Tramal, Tramedo, Zydol) may also be effective in some people with postherpetic neuralgia.[31]

Careful ongoing monitoring is required when opioids are used because of the lack of long-term follow-up studies regarding benefit, known opioid side effects and the potential for dependence.

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Corticosteroids

The role of corticosteroids in the management of herpes zoster remains controversial. While oral corticosteroids appear to be of benefit in the acute attack, they do not alter the incidence of postherpetic neuralgia.[3] The same appears to be the case for limited use of epidural methylprednisolone. Repeated epidural administration of corticosteroid and local anaesthetic has been shown in one trial to significantly reduce herpetic neuralgia;[32] however, the invasive nature of this approach has prevented its widespread use.

Topical lignocaine and capsaicin

Topical treatments are an attractive option in older patients (those aged over 60 years), who are more sensitive to systemic drug side effects. The two topical drugs most used worldwide are lignocaine

Table 4. Pharmacological treatments for persistent postherpetic neuralgia

Drug	NNT* (95% CI)[21]	Level of evidence[22]
Tricyclic antidepressants	2.6 (2.1–3.5)	I
Anticonvulsants		
• Gabapentin	4.4 (3.3–6.1)	I
• Pregabalin	4.9 (3.7–7.6)	I
• Sodium valproate	2.1 (1.4–4.2)	II
Opioids	2.7 (2.1–3.7)	I
Tramadol	4.8 (2.6–26.9)	II
Topical treatments		
• Lignocaine patches	–	II
• Capsaicin	–	I

* NNT = number needed to treat to achieve 50% reduction in pain.

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5% transdermal patches and capsaicin cream 0.025 to 0.075% (Zostrix, Zostrix HP). While there is growing interest in these treatments, strong evidence to support their use as first line therapies is lacking.[21,33] After a significant time off pharmacy shelves in Australia, topical capsaicin has returned to pharmacies as an unscheduled product. Lignocaine patches are not currently available in this country.

Effective use of capsaicin requires gradual introduction because of frequent uncomfortable burning sensations. Sorbolene cream may be used to dilute capsaicin prior to application, and improves its tolerability during introduction. Prior application of topical local anaesthetic (e.g. lignocaine plus prilocaine [EMLA]) may also improve initial success.

Nonpharmacological therapies

Neurostimulation

Spinal cord stimulation or peripheral nerve stimulation may provide a means for managing postherpetic neuralgia in the more severe cases.[34,35]

Cognitive behavioural therapy

To help people manage the challenge of persistent pain it is important to optimise their pain management skills. There is strong evidence to support the value of cognitive behavioural therapy (CBT) programs in people with persistent pain.[36] Such programs aim to reduce the effect of the pain on the persons function and mood.

In patients in whom initial medication measures fail to control pain, more formal assessment and management via a pain medicine specialist and pain team may be necessary. It is important to note that early referral results in better outcomes. If there are predictable delays in obtaining formal pain assessment, direct phone discussion with a specialist may be helpful. If access to a specialist team is not possible, referral to a clinical psychologist with pain expertise may suffice.

Books detailing the general principles of a pain program, written from a patient's point of view, are readily available. They are important self-help resources and can be used to prepare for a formal program. An example of such a book is *Manage Your Pain* by Michael Nicholas, Allan Molloy, Lois Tonkin and Lee Beeston (of the ADAPT Program at the University of Sydney Pain Management and Research Centre at the Royal North Shore Hospital), and published by ABC Books.[37]

Conclusions

The best treatment for postherpetic neuralgia remains prevention. The role of general practitioners remains crucial in this process. Adult vaccination to boost varicella zoster virus T-cell mediated immunity will become more widely used and promises to reduce the disease burden of this potentially devastating condition.

While no recent major breakthrough treatments have been discovered for the management of established postherpetic neuralgia, an expanded range of options has increased the likelihood of providing effective treatment in individual patients.

The goal of management is to increase activity and function. This is best achieved by combining both pharmacological and nonpharmacological strategies. Each drug prescribed must receive an adequate treatment trial prior to ascribing treatment failure. Poor response to treatment should prompt early referral or contact with a pain medicine specialist. MT

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST: None.

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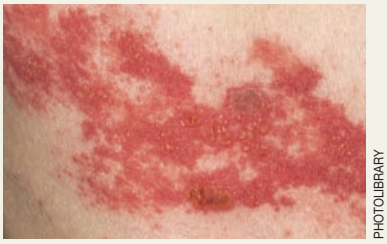

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