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Post-Herpetic Neuralgia in Older Adults

Evidence-Based Approaches to Clinical Management

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Abstract

Many individuals across the globe have been exposed to the varicella-zoster virus (VZV) that causes chickenpox. After chickenpox has resolved, the virus remains latent in the dorsal root ganglia where it can re-emerge later in life as herpes zoster, otherwise known as shingles. Herpes zoster is a transient disease characterised by a dermatomal rash that is usually associated with significant pain. Post-herpetic neuralgia (PHN) is the term used for the condition that exists if the pain persists after the rash has resolved. Advanced age and compromised cell-mediated immunity are significant risk factors for reactivation of herpes zoster and the subsequent development of PHN. Though the pathophysiology of

PHN is unclear, studies suggest peripheral and central demyelination as well as neuronal destruction are involved.

Both the vaccine against VZV (Varivax®) and the newly released vaccine against herpes zoster (Zostavax®) may lead to substantial reductions in morbidity from herpes zoster and PHN. In addition, current evidence suggests that multiple medications are effective in reducing the pain associated with PHN. These include tricyclic antidepressants, antiepileptics, opioids, NMDA receptor antagonists as well as topical lidocaine (lignocaine) and capsaicin. Reasonable evidence supports the use of intrathecal corticosteroids, but the potential for neurological sequelae should prompt caution with their application. Epidural corticosteroids have not been shown to provide effective analgesia for PHN. Sympathetic blockade may assist in treating the pain of herpes zoster or PHN. For intractable PHN pain, practitioners have performed delicate surgeries and attempted novel therapies. Although such therapies may help reduce pain, they have been associated with disappointing results, with up to 50% of patients failing to receive acceptable pain relief. Hence, it is likely that the most effective future treatment for this disease will focus on prevention of VZV infection and immunisation against herpes zoster infection with a novel vaccine.

1. Epidemiology

Herpes zoster or shingles is a common disease in the elderly, with an overall population incidence of 3 per 1000 per year rising to 10 per 1000 per year by 80 years of age.[1] Observations support the belief that a decline in cell-mediated immunity to the varicella-zoster virus (VZV) can lead to a higher incidence and severity of herpes zoster and post-herpetic neuralgia (PHN). There is an estimated 20% lifetime risk of developing herpes zoster.[2] The disease can ultimately affect up to half of all people who live to 85 years of age and lead to considerable morbidity.[3] Studies of the epidemiology of PHN indicate that the risk of having continued pain at 12 months is almost five times higher in patients who are 80 years of age compared with those <80 years of age. In fact, almost 50% of patients >70 years of age describe pain lasting >1 year after the onset of the PHN rash. The worldwide population is aging at an unprecedented rate. For instance, the proportion of the global population aged ≥65 years in the industrialised nations is projected to double from 15% today to nearly 30% by 2050.[4] Consequently, PHN may grow in prevalence and public health costs.

Herpes zoster is typically associated with a rash and concurrent or subsequent pain. PHN is a term that has been used for prolonged pain associated with herpes zoster. There are many definitions of PHN in terms of the onset and duration of pain. These range from pain sensed immediately after the resolution of the rash to pain persisting for ≥6 months following resolution of the rash. Such disparate definitions have made estimating the prevalence of the disease difficult, but current estimates indicate that >1 million people in the US suffer from PHN. In addition to age, other risk factors for progression to PHN include patients who experience more severe pain with acute herpes zoster, greater herpes zoster rash severity, greater neurosensory disturbances during acute zoster, the presence of zoster prodromal symptoms, a more pronounced zoster immune response, psychosocial distress and

immunocompromised state (including HIV and transplant recipients).[5]

2. Pathology, Pathophysiology and Clinical Features

Herpes zoster is caused by VZV, a virus composed of double-stranded DNA which is classified within the herpes family. Infection with this virus causes two distinct illnesses. The first is well known and is called chickenpox; this illness frequently occurs early in life and represents an initial VZV infection. Historically, most practitioners considered chickenpox a mild illness; however, clinicians now recognise that chickenpox can be dangerous and sometimes even fatal. Before the US introduced the VZV vaccine in 1995, approximately 4 million cases of chickenpox and 100 deaths were reported annually.[6,7]

The second illness, known as herpes zoster or shingles, usually occurs later in life and represents a reactivation of the original infection.[7] During the primary infection, the virus gains entry into the dorsal root ganglia (sensory nerve). The medical community has an incomplete understanding of how the virus enters the dorsal root ganglia and whether it resides in neurons or supporting cells. Nevertheless, subsequent to the initial infection, the virus remains latent, often for decades, because of the action of cell-mediated immunity that is acquired during the primary infection. The mechanism responsible for reactivation is thought to be secondary to development of an immunocompromised state, such as AIDS or an age-related decrement in immune status.[8] Reactivation of latent VZV from the dorsal root ganglia is responsible for neuronal damage and the classic dermatomal rash and pain that result from herpes zoster. Acute zoster causes cutaneous inflammation and partial denervation in a dermatomal distribution as well as inflammation, necrosis and fibrosis in the dorsal horn of the spinal cord.[6] The available evidence suggests that herpes zoster pain results from either deafferentation or from aberrant activity of the remaining sensitised peripheral nociceptors, or possibly from both pathophysiological processes.[9-11]

The typical clinical manifestation of herpes zoster is a vesicular rash displayed in a unilateral dermatomal distribution. Patients often notice the rash in the mid- to low thoracic region or the ophthalmic branch of the trigeminal nerve. Vesicles eventually become haemorrhagic and crust over within 7–10 days and sometimes produce residual scarring and pigmentary changes. Dissemination of herpes zoster to other cutaneous sites or to visceral regions is exceedingly rare in immunocompetent individuals.[12]

Herpes zoster is associated with a characteristic pain syndrome that can be divided into three types: prodromal pain (pain felt before lesions develop), pain associated with the lesions, and pain that persists after the lesions have cleared (and which may continue for the rest of the patient's life). Patients frequently describe prodromal pain as sharp and stabbing in nature with associated paraesthesias, burning dysaesthesias and pruritus in the affected dermatomal area.[3] Throughout this prodromal period, patients may be misdiagnosed with myocardial infarction, herniated disc or a variety of gastrointestinal and/or gynaecological disorders; therefore, prompt and accurate diagnosis is critical for proper treatment. After the herpes zoster vesicles erupt, patients usually complain of terrible pain in the affected area, often reporting it as unrelenting and burning/shooting in nature. When the vesicles recede and if patients complain of ongoing pain, the distinctive neuropathic pain state known as PHN ensues.

Though the pathophysiology of PHN remains elusive, postmortem studies in patients with PHN have found demyelination and axonal loss both in peripheral nerves and sensory roots.[13] Further, in patients with PHN-associated pain, researchers have

observed cell loss, demyelination with fibrosis and dorsal horn atrophy.[13] Other investigations suggest that deafferentation or aberrant peripheral nociceptors may account for the pain of PHN.[14-16] In fact, subtypes of PHN may be distinguished based on their neural mechanisms. Clinical signs of sensory loss, allodynia or deafferentation may facilitate the identification of these subtypes.[6] These subtypes include an irritable nociceptor group of patients who display mechanical allodynia (pain resulting from light touch on the skin) and normal sensation to thermal stimuli or thermal hyperalgesia; a deafferentation group who suffer from persistent pain in a region of sensory loss and no allodynia (anaesthesia dolorosa); and finally a central reorganisation group who present with mechanical allodynia and sensory deficits to thermal stimuli.[17] Unfortunately, this clinical differentiation strategy has little bearing on current treatment options.

3. Treatment

It has been difficult to evaluate the efficacy of the many treatments for PHN because clinical studies of these agents have been characterised by small sample size, heterogeneous populations, inadequate controls, ambiguous definitions of outcome and short duration of follow-up. Because PHN frequently resolves spontaneously over time, pain reduction may be incorrectly attributed to treatment.[6] There are many classes of drugs discussed in this review that may be effective and should perhaps be considered first-line treatments in PHN (table I, figure 1). Unfortunately, 50% of patients may not obtain satisfactory analgesia despite treatment with these medications.[18,19] More invasive procedures that lack proven efficacy may be incorporated into treatment strategies for those patients with pain that is refractory to more conservative and standard treatments.

3.1 Vaccines

PHN is a challenging disease to treat and investigations are underway to explore methods of preventing herpes zoster and its subsequent progression to PHN. Following primary VZV (community-acquired) infection, viral immunity declines with increasing age.[20] Consequently, the incidence of herpes zoster increases with age as cell-mediated immunity attenuates. The vaccine against VZV, Varivax® (Merck),[1] which is now routinely given to children, is expected to decrease the incidence of chickenpox and subsequent development of herpes zoster in this younger, vaccinated cohort; however, a large portion of the global population in their teens and older who have developed community-acquired chickenpox are still at risk for herpes zoster. Similar to the immunity which is acquired from primary VZV infection, that acquired from VZV vaccine (Varivax®) can be expected to decline during the process of aging. However, experience to date suggests that herpes zoster develops less frequently in individuals infected with varicella vaccine virus (Varivax®) than in those infected with community-acquired VZV. Prospective evaluation of individuals vaccinated during childhood will help confirm a decreased incidence of herpes zoster and PHN in later adulthood.

Investigators recently discovered sizeable benefits of vaccinating older adults with a higher potency form of the Varivax® vaccine than that currently used in the paediatric population to prevent varicella (chickenpox).[21] Specifically, a randomised, double-blind, placebo-controlled study examined 38 546 people >60 years of age who received either an experimental, live attenuated Oka/Merck VZV vaccine (later called Zostavax®) or placebo. Use of this vaccine was associated with a >50% reduction in the incidence of herpes zoster illness, an impressive 66% decrease in the incidence of PHN, and a

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

Table I. Summary of effective medications for post-herpetic neuralgia in older adults

Medication	Initial dosage	Titration	Adverse effects
Tricyclic antidepressants	10mg every evening	Increase by 10mg every 7 days to 50mg, then to 100mg and then to 150mg nightly	Sedation, xerostomia, confusion, dysrhythmia, weight gain, dizziness
Antiepileptics			
gabapentin	100mg three times daily	100–300mg increases every 5 days to total dose of 1800–3600 mg/day	Somnolence, dizziness, fatigue, ataxia
pregabalin	75mg twice daily	Increase to 150mg twice daily within 1 week	Somnolence, dizziness
Opioids			
oxycodone sustained-release	10mg every 12 hours	As needed for pain while balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, hormonal changes
transdermal fentanyl	12 μg/hour, changed every 3 days	As needed for pain while balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, skin irritation, hormonal changes
morphine sustained-release	15mg every 12 hours	As needed for pain while balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, hormonal changes
methadone	2.5mg three times daily	As needed for pain while balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, hormonal changes
transdermal buprenorphine	35 μg/hour, changed every 3 days	As needed for pain while balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, skin irritation, hormonal changes
Tramadol (immediate-release)	50 mg/day	Increase by 50mg every 3–4 days to total dose between 100–400 mg/day, divided dose	Nausea, emesis, dizziness, vertigo, somnolence, headache, constipation
Transdermal 5% lidocaine (lignocaine)	1–3 patches worn for 12 hours	None	Skin irritation
Lidocaine gel 5%	Apply to affected area	None	Skin irritation
EMLA®	Apply to affected area	None	Skin irritation
Capsaicin	0.025–0.075% cream or lotion applied to affected area	None	Localised burning sensation

EMLA® = eutectic mixture of local anaesthetics (lidocaine 2.5% and prilocaine 2.5%).

61% reduction in the burden of illness. The vaccine clearly does not eliminate the disease or treat active PHN. Nevertheless, the evidence highlights the substantial benefit of the vaccine in curtailing overall morbidity and disease-related costs of treating herpes zoster and PHN. On 25 May 2006, the US FDA licensed use of the live, attenuated VZV vaccine Zostavax® (Merck) to reduce the risk of herpes zoster in adults aged ≥60 years. Zostavax® is a higher potency form of the Varivax® vaccine. Researchers believe that the vaccine strengthens cell-mediated immunity and thereby protects older adults from developing herpes zoster and PHN.

3.2 Antivirals

Prompt treatment of herpes zoster with antiviral medications (aciclovir, for example) can reduce the symptoms of acute pain and may attenuate progression to PHN. These agents represent one of the most important therapeutic tools in the management of herpes zoster. While aciclovir has been the mainstay antiviral treatment for herpes zoster, several studies have evaluated newer agents such as valaciclovir and famciclovir.

Famciclovir 500mg three times daily has been found to be an effective and well tolerated treatment for acute herpes zoster.[22] Moreover, treatment with famciclovir was found to be associated with a 3.5

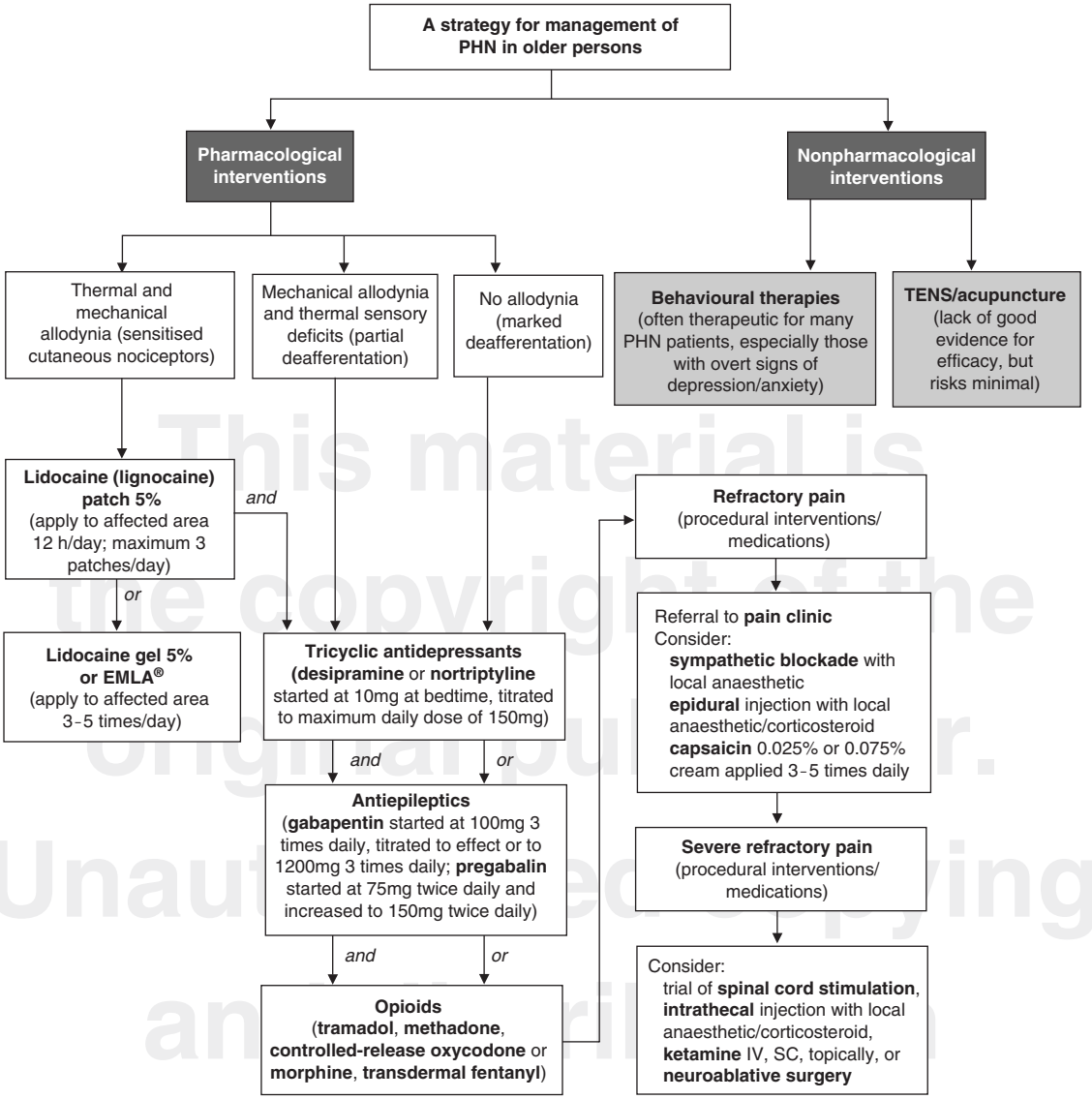

Fig. 1. Strategy for management of post-herpetic neuralgia (PHN) in older persons (adapted from Panlilio et al.,[6] with permission). **EMLA®** = eutectic mixture of local anaesthetics (lidocaine 2.5% and prilocaine 2.5%); **IV** = intravenously; **SC** = subcutaneously; **TENS** = transcutaneous electrical nerve (neural) stimulation.

month reduction in the median duration of PHN for patients aged ≥50 years when administered during acute zoster infection. A randomised, double-blind, placebo-controlled trial of two doses of famciclovir (500mg or 750mg three times daily) showed a significant reduction in pain at 5 months and a faster resolution of PHN with a median reduction of 2 months.[23] Famciclovir was well tolerated, with adverse events reported equally by treated patients and those given placebo. Furthermore, a recent randomised trial by Shafran and colleagues[24] evaluated cutaneous healing of herpes zoster with

famciclovir 750mg once daily, 500mg twice daily, 250mg once daily and aciclovir five times daily. The results showed equal effectiveness for each antiviral and dose in terms of healing cutaneous lesions and reducing acute herpes zoster pain. However, this study did not assess the effects of these treatment regimens on progression to PHN.

Valaciclovir was studied in a multicentre, randomised, three-arm, double-blind investigation and compared with aciclovir in patients ≥50 years of age with herpes zoster.[25] Valaciclovir was given in doses of 1000mg every 8 hours for 7 or 14 days and aciclovir in doses of 800mg five times daily for 7 days. The results demonstrated that valaciclovir significantly reduced the period of herpes zoster-associated pain compared with aciclovir (38 days vs 51 days, respectively), shortened the duration of PHN and lowered the proportion of patients experiencing pain at 6 months (19.3% vs 25.5%, respectively). No added benefits were observed by extending valaciclovir treatment from 7 to 14 days.

Both valaciclovir (1000mg three times daily) and famciclovir (500mg three times daily) were studied for 7 days in a randomised, controlled trial for the treatment of herpes zoster in patients ≥50 years of age.[26] Together, these antivirals showed equivalent efficacy in enhancing the resolution of zoster-related pain and PHN.

Aciclovir, valaciclovir and famciclovir are all safe and well tolerated antivirals that require adjustments only in patients with renal compromise. Valaciclovir and famciclovir may be preferred over aciclovir because of their simpler dosing schedules, although all three effectively treat herpes zoster-related pain and may attenuate the burden of PHN.

Recommended oral dosages of antivirals for herpes zoster based on high quality studies are valaciclovir 1000mg three times daily for 7 days; famciclovir 500mg three times daily for 7 days and aciclovir 800mg five times daily for 7–10 days.[27] Ideally, one of these medications should be initiated within 72 hours of onset of the lesions; however, current evidence suggests that patients will still benefit from antiviral therapy even if treatment is delayed beyond 3 days.[28,29]

In summary, incorporating antiviral therapy as an initial step in treatment for older patients presenting with herpes zoster is critical to controlling their symptom burden.

3.3 Corticosteroids

Some clinicians have advocated the use of oral corticosteroids as a treatment modality for herpes zoster and PHN. For instance, one study using a combination of prednisone and aciclovir to treat herpes zoster reported a significant reduction in pain and improved quality of life in healthy patients >50 years of age.[30] However, this study and another randomised, double-blinded, placebo-controlled trial concluded that administration of corticosteroids for 21 days did not prevent the development of PHN.[30,31] Hence, the evidence fails to support the use of oral corticosteroids as a prophylactic agent against the onset of PHN.

3.4 Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) have been utilised for several years in the treatment of neuropathic pain, following publication of randomised, controlled trials that have documented the analgesic property of TCAs irrespective of their antidepressant effect (table II). TCAs inhibit the reuptake of serotonin and norepinephrine at presynaptic nerve terminals and facilitate the descending antinociceptive pain pathway. In addition, TCAs may confer added benefit to PHN patients through their sedative properties (antihistaminergic) and anxiolytic actions,[32] given that PHN as well as other chronic pain conditions can induce sleep disturbances and anxiety. Both the tertiary amines (amitriptyline, doxepin) and the secondary amines (desipramine, nortriptyline) are used in clinical practice.

Table II. Post-herpetic neuralgia (PHN) pharmacological efficacy data

Analgesic agent	NNT (95% CI)	Reference
TCAs	2.1 (1.7, 3.0)	21
Gabapentin	2.8 (NR)	3
Pregabalin	3.6 (2.4, 6.9)	33
Opioids[a]	2.67 (2.07, 3.77)	34
Tramadol	4.7 (2.9, 19.0)	35
5% Lidocaine (lignocaine)[b]	4.4 (2.5, 17.5)	36
Capsaicin	3.2 (2.1, 6.3)	37

a Pooled data.

b Peripheral neuropathic pain syndrome pooled data (22/40 with PHN).

NNT = number needed to treat; **NR** = not reported; **TCAs** = tricyclic antidepressants.

The number of patients who must be exposed to an intervention before the clinical outcome of interest occurs (e.g. the number of patients needed to treat in order to prevent one adverse outcome) is described as the number needed to treat (NNT). Three randomised, controlled trials comparing the use of antidepressants versus placebo to treat PHN have demonstrated their efficacy with an NNT of 2.1 (95% CI 1.7, 3.0) for at least 50% pain relief.[38]

Both nortriptyline and amitriptyline have been studied in a randomised, double-blind, crossover trial and found to reduce PHN pain measured by the visual analogue scale (VAS).[39] Patients reported that treatment with each medication provided effective pain control and 67% of each group said that they experienced at least a good response to treatment. Based upon strong clinical evidence, the TCAs (amitriptyline, nortriptyline and desipramine) effectively reduce the pain associated with PHN.[9,39]

Because adverse effects are more common with the tertiary amines (amitriptyline, doxepin), the secondary amines nortriptyline and desipramine should be strongly considered for use in the older population. However, in this select population, even these medications may be associated with a poor adverse effect profile, mainly because of their anticholinergic activity.[40] For instance, patients taking TCAs typically complain of fatigue and dry mouth and may report constipation, imbalance, falls, urinary retention and palpitations. Other adverse effects may include orthostatic hypotension (α_1-adrenoceptor antagonism), weight gain (antihistaminergic), nausea, blurred vision, confusion and dizziness. TCAs can also cause significant dysrhythmias in patients with conduction abnormalities, which is perhaps due to their capacity to block sodium channels or their anticholinergic properties. For instance, a number of cases report a link between TCAs and QT prolongation, torsades de pointes and sudden cardiac death.[41] Hence, clinicians should prescribe TCAs cautiously to patients with a history of congenital QT syndrome, cardiovascular disease or hypokalaemia.[41] Fortunately, adverse effects are often dose-related and less pronounced when low doses are titrated slowly ('low and slow' concept). A rational dose administration regimen for the TCAs consists of 10mg by mouth before bedtime, gradually increasing by 10mg every week to an initial target dose of 50mg by mouth at bedtime.[42] If patients do not develop intolerable adverse effects and experience inadequate pain relief, the dose can be escalated in 10mg increments until a maximum dose of 150mg at bedtime is reached. Many older adults may only tolerate maximal doses of 100mg. Relevant contraindications to TCAs include recent heart attack, epilepsy, narrow-angle glaucoma, heart block, urinary retention and use of monoamine oxidase inhibitors.

In summary, the evidence demonstrates that TCAs are effective agents for treating PHN. Only limited evidence supports the use of nortriptyline over amitriptyline.[39] However, amitriptyline can be associated with significant adverse effects in the elderly compared with nortriptyline and desipramine,[43] and practitioners should therefore consider initial treatment with the secondary amines.

3.5 Antiepileptics

Gabapentin has become a widely used medication for the treatment of PHN over the past 5 years. This drug was designed as a centrally acting GABA agonist with ability to transfer across the blood-brain barrier and treat partial seizures.[44] Interestingly, it appears to have no effect at GABAminergic receptors. Instead, gabapentin binds to a protein in cortical membranes with an amino acid sequence that resembles the $\alpha 2\delta$ subunit of voltage-gated calcium channels, with a consequent reduction in neurotransmitter release. However, its precise mechanism of action remains unknown. Gabapentin is absorbed after ingestion and is not metabolised. Hence, the medication is excreted unchanged, primarily in the urine. There are no known interactions between other antiepileptics and gabapentin.[44]

Gabapentin has been well studied for the treatment of PHN in at least two large, double-blind, placebo-controlled trials. In the first, Rowbotham et al.[45] in 1998 studied 225 patients who received a 1-month titration of gabapentin and another 1 month of treatment with other medications at a stable, unchanged dose. Eighty-three percent of patients received gabapentin ≥2400 mg/day and 65% received 3600 mg/day. Patients in the gabapentin-treated group had significantly reduced daily pain scores in addition to improved sleep. For instance, 66 of 94 patients reported improvement in pain with an NNT of 2.8 for moderate improvement and a number needed to harm (NNH) of 10.3. NNH measures the number of patients who require a specific treatment in order to cause harm in one patient.

In 2001, Rice and Maton[46] studied 334 patients in a randomised, double-blind, placebo-controlled trial. Patients in this study received gabapentin at doses of 1800 mg/day or 2400 mg/day or placebo. One-third of subjects in the gabapentin-treated group (regardless of dose) reported ≥50% reduction in pain compared with 14% in the placebo group. No differences in response rate or adverse effect rate were detected between the two gabapentin doses. The investigators concluded that gabapentin treatment led to significant improvements in multiple validated pain and quality of life measures and was associated with few and generally mild adverse effects. In 2002, the FDA approved gabapentin as an agent for the treatment of PHN.

Overall, gabapentin is well tolerated.[44] Frequently reported adverse effects are somnolence and dizziness, and sometimes ataxia and fatigue. These effects often resolve within 2 weeks of commencement of treatment.[44] A reasonable starting dose in an older patient may be 100mg three times daily with 100–300mg increases every 5 days or so. The median effective range is 900–1200 mg/day but some patients may tolerate up to 3600 mg/day, given in divided doses three times daily.[40] The dose may need to be adjusted for patients with renal insufficiency given that excretion occurs predominantly through the kidneys.

Pregabalin, recently approved by the FDA for the treatment of PHN and diabetic peripheral neuropathy, also acts at the $\alpha 2\delta$ subunit of voltage-gated calcium channels in a similar manner to gabapentin. Interestingly, pregabalin has been shown to have greater analgesic properties than gabapentin in rodent models of neuropathic pain.[47] In two large randomised, placebo-controlled trials, pregabalin was shown to be efficacious for reducing the pain of PHN.[33,48] In one study, pregabalin 600 mg/day resulted in a ≥50% reduction in pain compared with 20% pain relief with placebo.[48] Adverse effects (dizziness, somnolence) were similar to those reported for gabapentin. The titration schedule for pregabalin is more rapid and easier to follow from a patient's perspective. The starting dose is 75mg twice daily, increasing to 150mg twice daily within 1 week if the patient is tolerating the medication. If the patient still fails to experience sufficient relief, the dose may be increased to 300mg twice daily, assuming the adverse effect profile is favourable.

Several randomised, placebo-controlled studies of pregabalin therapy for PHN haved reported rapid onset of pain reduction within the first week of treatment.[33,48,49] In clinical practice, a favourable response to the medication may require 2 weeks of treatment.

3.6 Opioids

Although the efficacy of treatment of PHN with opioids has been a subject of controversy, mounting evidence strongly supports their value for alleviating PHN pain.[9,10,50,51] A recent review article indicates that short-term studies provide only equivocal evidence that treatment with opioids is effective in reducing the intensity of neuropathic pain in PHN.[52] However, the same review notes that several studies of intermediate length show that opioids significantly reduce PHN pain compared with placebo. It has also been suggested that higher doses of opioids produce a greater reduction in the intensity of pain than lower doses. At the same time, these higher doses are associated with a less favourable adverse effect profile.[53]

In a randomised, placebo-controlled, crossover trial comparing the efficacy of opioids with those of TCAs and placebo in patients with PHN, the investigators found that opioids and TCAs produced greater pain relief than placebo (38%, 32% and 11% pain relief, respectively).[9] There was a trend toward greater pain reduction and a lower NNT with opioids compared with TCAs, and sustained-release morphine was more effective in decreasing PHN pain than nortriptyline. Furthermore, older patients preferred opioids to TCAs (54% preferred opioids compared with 30% who preferred TCAs and 16% who preferred placebo), they tolerated the opioids well, and they did not experience significant cognitive deficits with use of sustained-release morphine.[9]

Controlled-release oxycodone was evaluated in a randomised, placebo-controlled, double-blind, crossover trial and shown to reduce persistent PHN pain by 50% compared with placebo among the 22 of 38 patients who completed the study.[10] The discontinuation rate was 24% and only one patient discontinued treatment because of opioid-induced adverse effects; lack of treatment response was the reason in the remainder.

Buprenorphine, a partial μ agonist, κ antagonist and δ antagonist,[54-56] may have emerging therapeutic value in treating neuropathic pain in humans. For instance, four recent case studies in patients with neuropathic pain or nociceptive pain with significant neuropathic features reported sufficient pain relief without undue adverse events in patients treated with transdermal buprenorphine in doses of either 35 μg/hour or 79 μg/hour.[57] Furthermore, an open-label, long-term follow-up study (up to 5.7 years) in 239 cancer and non-cancer patients who had participated in a previous double-blind, placebo-controlled, transdermal buprenorphine study found that 47.3% experienced satisfactory pain relief, 38.9% reported good pain relief and 3.8% described complete pain relief with buprenorphine treatment (35 μg/hour changed every 3 days).[58] Adverse events and tolerability were both acceptable. Neuropathic pain accounted for 26% of the non-cancer pain diagnoses and PHN represented 3% of the neuropathic pain population. Future randomised, controlled studies with buprenorphine in patients with PHN will aid in confirming its utility in alleviating neuropathic pain.

A recent randomised, double-blind, active-placebo controlled crossover study compared combined treatment with sustained-release morphine and gabapentin with each medication used separately in patients with PHN and painful diabetic neuropathy.[59] Forty-one patients completed all four treatment periods: 16 patients had PHN and 25 patients had diabetic neuropathy. Combined treatment with morphine-gabapentin produced greater pain relief in both neuropathic pain states than either single agent

alone or placebo. Moreover, patients reported beneficial effects of combined therapy on pain-related interference with daily activities, mood, and health-related quality of life. Combination therapy did produce a higher frequency of constipation and sedation than gabapentin alone and a higher frequency of dry mouth than morphine alone. This trial is unique in suggesting superior efficacy of dual therapy with gabapentin and morphine in the treatment of neuropathic pain.

Several opioid formulations exist for outpatient treatment of chronic pain and most experts agree that the formulation and dosing methodology should be customised to the patient's pain intensity, comorbidities and lifestyle. Sustained-release morphine, oxycodone and transdermal fentanyl may be preferable to methadone, especially in the older population, given the prolonged and unpredictable half-life of methadone as well as age-related decrements in renal clearance and hepatic metabolism. However, animal studies[60,61] have demonstrated the NMDA receptor antagonist properties of methadone, which may therefore be a reasonable choice for treatment of neuropathic pain (e.g. PHN). Moreover, methadone may be a useful alternative to brand name opioids because of the lower risk of diversion of this medication and its lower cost.

Based on clinical experience, reasonable starting doses of long-acting opioids in older patients who are opioid-naive include methadone 2.5mg by mouth three times daily, sustained-release oxycodone 10mg by mouth every 12 hours, sustained-release morphine 15mg by mouth every 12 hours or transdermal fentanyl 12 μg/hour every 3 days. The goal of opioid therapy consists of achieving a balance between analgesia and intolerable adverse effects; therefore, no maximal dose for opioid therapy can be recommended. The dose should be individualised for each patient.

Opioid use is often associated with adverse effects such as nausea, constipation, sedation, hormonal changes, immunological alterations, hyperalgesia and impaired cognitive function,[62] all of which may be exaggerated in older persons. Constipation represents a common and potentially debilitating adverse effect in this age group. Furthermore, because tolerance to the constipative effects of opioids rarely develops, concurrent treatment with laxatives is important. Current theory regarding the aetiology of constipation implicates opioid-induced peripheral μ-receptor stimulation in the enteric nervous system as well as CNS changes that disrupt autonomic outflow to the gut. Typical management consists of nonpharmacological strategies, such as increasing dietary fibre, fluid intake, mobility and ambulation, and pharmacological approaches, such as use of a stool softener and stimulant laxative (docusate sodium and senna) and/or osmotic agents (magnesium hydroxide, mineral oil, methylcellulose, polyethylene glycol, sorbitol) or prokinetic agents (metoclopramide) if symptoms are related to delayed gastric emptying.

Tolerance to other opioid-induced adverse effects such as nausea, sedation and cognitive dysfunction usually develops in advance of tolerance to the analgesic property of opioids. If adverse effects persist, clinicians may consider rotating to another opioid, discontinuing the opioid or incorporating targeted treatments based on symptomatology. For example, metoclopramide, dimenhydrinate, ondansetron, prochlorperazine or transdermal scopolamine may be useful in treating nausea/vomiting; caffeine, dextroamphetamine, methylphenidate or modafinil may help counter sedation; and opioid rotation or opioid discontinuation may offer the best solution to persistent cognitive dysfunction. In rare cases, haloperidol may be used to manage delirium and a benzodiazepine may be added to treat agitation.

Many clinicians agree that initiating low dose opioid therapy followed by slow titration to achieve meaningful analgesia (enhanced quality of life)

should be the goal of therapy. Dose escalation coupled with comprehensive and ongoing assessment of responsiveness, adverse effects and aberrant behaviour (e.g. diversion or self-escalation) should also be integral to opioid treatment.

3.7 Tramadol

Tramadol, a synthetic derivative of codeine, is a centrally-acting analgesic that shares properties of opioids and TCAs. Specifically, tramadol acts as a weak μ-receptor agonist, inhibits the reuptake of serotonin and norepinephrine, and facilitates neuronal serotonin release. In fact, the evidence suggests that the effect of tramadol on levels of serotonin and norepinephrine may potentiate endogenous descending inhibitory pain pathways.[63-66] Tramadol modulates spinal pain transmission by indirectly activating post-synaptic α2 adrenergic receptors, which prevents impulses from reaching the brain.[67] The multi-mechanistic properties of tramadol produce centrally-mediated antinociception. Tramadol has been shown to be effective for the treatment of painful diabetic neuropathy[68] and PHN.[35] In a multicentre, randomised, double-blind, placebo-controlled trial,[35] there was a higher percentage of pain relief and decreased use of breakthrough medications in the immediate-release tramadol group compared with placebo. More specifically, 49 of 63 patients receiving tramadol reported >50% reduction in pain compared with 35 of 62 patients receiving placebo. The NNT for tramadol was 4.7 (95% CI 2.9, 19.0). One non-controlled study also suggested that immediate-release tramadol may be effective in reducing PHN pain while avoiding the adverse effects linked with more potent opioid agonists.[69]

Administration of immediate-release tramadol in older adults should be initiated at 50 mg/day and gradually increased by 50mg increments every 3–4 days to diminish the onset of adverse events.[70] The usual effective dose ranges from 100 to 400 mg/day, given in divided doses four times daily. Long-term use of tramadol is not associated with a risk of psychological dependence,[71] and abuse liability is low, probably because the drug binds weakly to the μ opioid receptor, has a slow onset of action and blocks norepinephrine reuptake.[72] Such properties lead to a reduced frequency of euphoria and, therefore, misuse. Furthermore, compared with typical opioids, tramadol offers low potential for precipitating respiratory depression.[73]

A controlled-release preparation of tramadol, tramadol ER (100mg, 200mg and 300mg), is now available for the treatment of pain. There are no studies on the effectiveness of this form of tramadol in patients with PHN. However, one recent multicentre, randomised, double-blind, placebo-controlled trial reported a substantial reduction in pain and a significant improvement in physical function among patients with osteoarthritis.[74] There appears to be no ceiling dosage for analgesia and older adults seem to tolerate tramadol well.[40,73]

Typical adverse effects of tramadol may include nausea, vomiting, dizziness, vertigo, constipation, somnolence and headache.[67,75-77] Clinicians should also be mindful of the potential for elevated seizure risk or serotonin syndrome while patients are concurrently using tramadol with selective serotonin reuptake inhibitors, selective monoamine oxidase inhibitors or TCAs. This syndrome is a consequence of inhibition of serotonin reuptake by tramadol. The clinical triad of serotonin syndrome consists of cognitive/behavioural changes manifesting as agitation or restlessness; autonomic instability in the form of fever, tachycardia, diarrhoea or diaphoresis; and neurological changes such as hyperreflexia, shivering, clonus, myoclonus or tremors.[78] Treatment is primarily supportive with volume repletion and benzodiazepines, if necessary.

3.8 Topical Lidocaine (Lignocaine)

The lidocaine (lignocaine) patch consists of a 10 × 14cm, nonwoven, polyethylene-backed and medication-containing adhesive of 5% lidocaine (700 mg/patch) with other inactive ingredients. The patch can be cut to conform to specific painful areas on the intact skin.

Unlike other formulations of lidocaine, the lidocaine patch produces an analgesic effect without causing local anaesthesia; that is, the skin underlying the patch continues to have normal sensation (i.e. no "numbness").[79] The exact mechanism behind this effect is not known. One theory suggests that the formulation delivers sufficient amounts of lidocaine to block sodium channels in small, damaged or sensitised pain fibres, but insufficient amounts to block sodium channels in large myelinated A-β sensory fibres. The amount of lidocaine absorbed is directly proportional to the surface area of skin covered and to the duration of patch application.

Topical lidocaine in the form of a 5% patch has proven to be effective in reducing pain and allodynia associated with PHN in three randomised, controlled trials.[79-82] In fact, the protection afforded by the topical lidocaine patch itself against mechanical irritation of sensitised skin is of value irrespective of the pain-relieving pharmaceutical benefits. Also, lidocaine gel 5%,[83] and a eutectic mixture (lidocaine 2.5% and prilocaine 2.5%) of local anaesthetics (EMLA®)[84] applied to areas of pain and allodynia, can significantly reduce constant pain as well as paroxysmal pain and allodynia. Continued application over several days can provide additional benefit beyond the acute relief obtained with initial use.

The lidocaine patch offers the best relief of irritation in patients with marked allodynia and without sensory loss associated with PHN. Unlike systemic analgesics, topical local anaesthetics can lower pain in PHN without the threat of significant systemic effects. Consequently, cutaneous lidocaine offers promise as an excellent adjunctive therapy in older patients who are generally more susceptible to the adverse effects of systemic medications. In practice, many patients report partial relief, and complete relief is rare. Some patients must discontinue therapy because of local skin irritation.

The FDA approved use of topical lidocaine for the treatment of PHN in 1999. The current recommendation indicates a maximum of three patches to be worn for no longer than 12 hours over a 24-hour period.[85] Emerging data suggest that prolonged use of the patch may be beneficial in neuropathic pain. For instance, continuous 24-hour application of a maximum of four lidocaine patches in patients with low back pain and osteoarthritis was found to be safe and well-tolerated.[86,87] Clinicians should be aware that patients may require 2 weeks of therapy to determine whether the patch will confer meaningful benefit.

3.9 Capsaicin

Capsaicin is an alkaloid extracted from hot chilli peppers. It is available in the US as a cream or lotion in strengths of 0.025% and 0.075%. One proposed mechanism of action of capsaicin includes release of substance P and other neuropeptides from nociceptive fibres (unmyelinated C fibres). With repeated capsaicin use, continual release of substance P depletes neuronal stores of neurotransmitters, leading to inactivation of local nociceptive function and therefore analgesia.[88-90] Alternatively, human studies have shown that topical capsaicin causes damage to underlying nociceptive peripheral nerves. This discovery has lead investigators to conclude that capsaicin may induce neurodegenerative changes that promote pain relief.[91]

Capsaicin has been shown to be effective in reducing pain associated with PHN in two randomised trials.[37,92] Watson et al.[92] conducted a 6-week, randomised, double-blind, placebo-con-

trolled study of 0.075% capsaicin and reported a reduction in pain on the VAS in 48 of 74 patients receiving capsaicin (NNT = 3.2; 95% CI 2.1, 6.3). The maximum benefit was a 23% decrease in VAS pain from baseline after 4 weeks. Sixty percent of patients using capsaicin complained of burning compared with 30% receiving placebo. Ninety-three percent of patients in the 2-year open-label continuation of the study reported maintenance of pain relief.[92] Several patients enjoyed significant and prolonged improvement in pain symptoms and functional measures. No serious adverse effects of capsaicin therapy were reported.

The cream or lotion formulations of capsaicin can be applied 3–5 times daily in a 0.025–0.075% preparation. Use of capsaicin may be somewhat limited by the discomfort and burning sensation associated with initial nociceptor activation. However, capsaicin is not associated with systemic adverse effects and therefore may serve as a beneficial adjunct to other pain relief modalities in older people with PHN.

3.10 Ketamine

Ketamine, a non-competitive NMDA receptor antagonist, attenuates pain by preventing the activation of NMDA-associated calcium channels, which contribute to the "wind-up" phenomenon of central sensitisation.[93,94] Ketamine can be given intravenously, subcutaneously, orally, rectally or topically. Small trials in PHN patients have demonstrated that intravenous and subcutaneous infusions of ketamine can decrease both spontaneous and paroxysmal pain as well as allodynia.[11,95] Specifically, the five patients in one study[11] who received continuous subcutaneous infusions reported meaningful pain relief as well as significant adverse effects such as itching, painful induration at the injection site, frequent nausea, fatigue and dizziness. These adverse effects often limit the percutaneous use of ketamine. Other recognised problems that reduce the clinical utility of ketamine, especially in the elderly, include psychodysleptic (hallucinogenic) and cognition-impairing effects.

In a retrospective study of 16 patients, topical ketamine reduced pain associated with PHN without general systemic absorption and consequent adverse effects.[96] In case studies, one patient reported long-lasting relief from PHN-related pain using ketamine in multiple forms,[97] and another patient described pain relief without adverse effects from oral ketamine.[98]

Although there is no convincing evidence that ketamine can be used successfully for pain relief in PHN, emerging data highlight its potential application in this population. Perhaps an oral combination therapy that incorporates ketamine, a benzodiazepine, and a muscarinic receptor antagonist may mitigate the poor systemic adverse effect profile of ketamine, thereby enhancing its clinical effectiveness as an analgesic.

3.11 Intrathecal and Epidural Corticosteroids

Patients reported significant analgesia in a randomised, double-blind, controlled trial of intrathecal medications conducted by Kotani et al.[99] These investigators evaluated 277 patients with intractable (failed conventional treatments) PHN for 38 ± 19 months after randomising them to a control group not receiving lumbar puncture, a group that received 3mL of 3% intrathecal lidocaine, and a group that received preservative-free intrathecal methylprednisolone 60mg in 3mL of 3% lidocaine (methylprednisolone is not approved for intrathecal use by the FDA and preservative-free methylprednisolone is not available in the US). In this study, 90% of patients receiving methylprednisolone in lidocaine experienced good to excellent pain relief in addition to a reduction in their use of NSAIDs. Furthermore, these patients reported the same magnitude of analgesia through 2 years of follow-up (NNT = 1.3; 95% CI 1.2, 1.5), during

which there were also no observed complications of therapy.

While Kotani et al.[99] reported no neurological sequelae with use of intrathecal corticosteroids, data from case series of patients receiving intrathecal methylprednisolone for non-PHN conditions indicate risks such as chemical meningitis, chronic arachnoiditis and transverse myelitis.[100] Moreover, there have been several reports of arachnoiditis in multiple sclerosis patients receiving frequent intrathecal corticosteroid injections. Abram[101] has also discussed complications such as aseptic meningitis, bacterial meningitis, cauda equina syndrome and cerebral vein thrombosis associated with intrathecal corticosteroid administration.

The efficacy of epidural corticosteroid use in PHN patients was studied by Kikuchi et al.[102] They conducted a randomised, controlled, single-blind study of four intrathecal or epidural injections of preservative-free methylprednisolone 60mg at 1-week intervals. Although no benefit was seen in the epidural group, substantial relief was reported by the intrathecal group at 1 and 24 weeks following completion of the study (NNT = 1.4; 95% CI 1.0, 2.1).

Based on supportive, albeit limited, evidence from the most well-designed studies described in this section, intrathecal methylprednisolone is effective in alleviating PHN pain. However, clinicians should consider using this treatment only in refractory cases, given the potential risks of neuraxial pathology. In the US, clinicians should consider the medico-legal consequences of using a non-FDA approved medication intrathecally and be aware that obtaining preservative-free methylprednisolone may be difficult.

3.12 Sympathetic Blockade

The role of sympathetic blockade with local anaesthetics in the treatment of PHN has been reviewed by Wu et al.[103] in 2000 and Opstelten et al.[104] in 2004. It appears that these techniques may have a role in treating pain associated with acute herpes zoster and perhaps in reducing the incidence of PHN. However, sympathetic blockade has failed to provide sustained relief in patients with established PHN.[103,104] This failure of efficacy may be due to the partial rather than complete role of the sympathetic nervous system in contributing to pain and allodynia associated with PHN.

3.13 Other Therapies

There are cases of severe intractable PHN in which physicians have resorted to surgery. There is anecdotal evidence for efficacy of skin excision, sympathectomy, dorsal root entry zone lesions, cordotomy, thalamotomy, cingulumotomy and deep brain stimulation.[2,105] Many of these therapies reflect more extreme treatment options with potentially severe complications; therefore, all other options should be exhausted before considering neurosurgical interventions.

Both retrospective and prospective case series document satisfactory pain relief over a 2.4- to 3.8-year interval with spinal cord stimulation in patients with unrelenting PHN.[106,107] Although the level of evidence is low, both of the cited studies suggest that spinal cord stimulation may offer an alternative approach to pain control in patients who fail to derive acceptable relief from pharmacological, alternative and injection therapies.

There are also many alternative therapies that have been attempted and reported as successful, though none can be recommended because of lack of evidence in their favour. Some of these treatments include acupuncture, transcutaneous electrical nerve stimulation and topical benzydamine, geranium or peppermint oil. Because there is probably little risk associated with these treatments, their use may be considered in the older population when all conventional treatments have failed.

4. Conclusion

The incidence of herpes zoster increases with age and the prevalence of herpes zoster will escalate as the worldwide population ages at a very rapid rate. The most frequent complication of herpes zoster, PHN, ranks as one of the most intractable neuropathic pain disorders. Multiple medications have been evaluated in clinical trials and are associated with a reduction in PHN-related pain. Clinically, practitioners and patients alike struggle to blend pharmacological and interventional therapies in a way that provides truly meaningful pain relief and an enhanced quality of life to patients with PHN. Practitioners should customise their medical recommendations based on the patient's underlying health status, current medication regimen and tolerance for potential adverse effects. The recently released vaccine Zostavax® holds promise as a prophylactic strategy against the development of PHN. Novel research methods that can uncover risk factors related to the transition from herpes zoster to PHN will enhance the development of targeted preventative therapies. Furthermore, innovative strategies may someday permit the development of genetic regenerative therapies that can target damaged neurons and restore healthy function. The goal of all treatment approaches for PHN should centre on lessening the personal suffering and public health burden associated with this debilitating condition.

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