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Treatment of Postherpetic Neuralgia
An Update

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Contents

Abstract

Postherpetic neuralgia (PHN) is a chronic pain syndrome that is often refractory to treatment and can last for years, causing physical and social disability, psychological distress, and increased use of the healthcare system. In this paper we provide an update on recent developments in the treatment of PHN. We emphasise the results of recent studies that provide an evidence-based approach for treating PHN that was not available until very recently. In randomised, controlled clinical trials, the topical lidocaine patch, gabapentin, and controlled release oxycodone have been shown to provide superior pain relief in patients with PHN when compared with placebo. It has also recently been demonstrated that the tricyclic antidepressant nortriptyline provides equivalent analgesic benefit when compared with amitriptyline, but is better tolerated. Based on these results, nortriptyline can now be considered the preferred antidepressant for the treatment of PHN, although desipramine may be used if the patient experiences unacceptable sedation from nortriptyline. The topical lidocaine patch, gabapentin and controlled release oxycodone all appear to be as effective as tricyclic antidepressants in

the treatment of patients with PHN, and the results of these recent studies suggest that each of these treatments should be considered early in the course of treatment. Additional controlled trials are needed to compare the efficacy and tolerability of these 4 treatments – tricyclic antidepressants, gabapentin, the topical lidocaine patch and controlled release opioid analgesics – used singly and in various combinations in the treatment of patients with PHN.

The onset of herpes zoster ('shingles') is marked by a prodrome of dermatomal pain in the majority of patients. In almost all patients, a dermatomal rash appears within several days, and this rash is typically accompanied by pain. Although the zoster rash usually heals within 2 to 4 weeks, the nature and duration of the pain vary greatly. In a percentage of patients, pain in the affected dermatome persists after the acute infection and healing of the rash. Pain that persists beyond a defined interval is termed postherpetic neuralgia (PHN). This pain syndrome is often refractory to treatment and can last for years, causing physical and social disability, psychological distress, and increased use of the healthcare system.

In this paper we provide an update on recent developments in the treatment of PHN. Because excellent literature reviews of this topic have appeared,[1,2] we emphasise recent studies and update our own previous review of this material.[3] We begin by briefly discussing the natural history of herpes zoster pain, emphasising the findings most relevant to evaluating and treating patients with PHN.

1. Natural History of Herpes Zoster Pain

A variety of definitions of PHN have been proposed. Some authors have defined it as any pain persisting after the herpes zoster rash has healed.[4,5] Others have defined it as pain persisting beyond a specified interval following rash onset – for example, 4 weeks[6] or 3 months[7] – or as pain persisting beyond a specified interval after rash healing, for example, 3 months.[8,9]

Because the number of patients with pain declines with time, estimates of the proportion of patients with acute herpes zoster who develop PHN range from 9 to 34% and vary depending on the definition of PHN used.[10] Perhaps the most useful data for estimating the risk of PHN are provided by the results of a meta-analysis of the results of 14 placebo-controlled trials of acyclovir.[11] Of the patients with herpes zoster studied in the placebo groups in these trials, 22% had pain that persisted at least 3 months, a duration of pain that is consistent with definitions of PHN that consider it a chronic pain syndrome. However, 3 antiviral medications – acyclovir, famciclovir and valacyclovir – are now widely used in the treatment of patients with acute herpes zoster, and there is evidence that these medications reduce the risk of developing PHN and the overall duration of pain.[12-16] It is therefore likely that at present fewer than 22% of patients with acute herpes zoster will still have pain 3 months or more after rash onset.

Until recently, it was believed that there were no pain-free intervals in patients with PHN. However, there is now evidence that pain in PHN can be discontinuous, with pain-free intervals of varying durations occurring.[17-19] For example, in a study of 156 patients with PHN, '25% of patients with a poor outcome said that they could recall a time after the rash when they had little or no pain for a period of weeks to as much as 12 months'.[17]

For many years, older age was the only factor that had been consistently associated with an increased risk of developing PHN in patients with herpes zoster.[20,21] PHN is infrequent in patients under the age of 40 years, but common in older patients; as many as 75% of patients over the age of 70 years have pain at 1 month after healing and approximately 50% continue to have pain at 1 year.[20] In addition to age, 4 risk factors for PHN have now been identified by independent groups of investigators: greater acute pain severity, greater rash severity, sensory dysfunction in the affected dermatome during acute herpes zoster, and the presence of a painful prodrome preceding the rash.[10,22] Of

these risk factors, the most well established is greater acute pain severity. The results of a considerable number of recent studies have demonstrated that patients with more severe pain during acute herpes zoster are at greater risk for prolonged pain.

Four additional risk factors – more pronounced humoral and cell-mediated immune responses, fever, generalised impairment of large fibre afferents, and psychosocial distress – have been identified either in a single study or by a single group of investigators and therefore await replication by others. With respect to sex and dermatome, the literature is inconsistent, with some studies finding that females and patients with trigeminal zoster are at increased risk for the development of PHN and other studies finding no evidence in support of these relationships.[10,22]

In patients with PHN, 'alterations in mood, personality, activity levels, and social interactions are common'.[23] As is true of other chronic pain syndromes, patients with PHN can develop depression as well as physical, occupational and social disability as a consequence of their unremitting pain.[24] In a recent study, it was reported that 59% of a sample of patients with PHN attending a pain clinic in Liverpool, England, had taken time off from their usual activities and that these patients had been prevented from pursuing these activities for up to 16 years, with the average being 1.4 years.[25] In another study of the psychosocial impact of PHN, patients who had PHN for longer than 6 months were found to have greater disability and psychological distress than those who had PHN for less than 6 months.[26] The results of this study suggest that psychosocial distress may increase the longer that PHN persists, although it is also possible that prolonged pain is a consequence of greater distress. Not surprisingly, there is also evidence of substantial utilisation of a variety of healthcare resources by patients with PHN. For example, it has been reported that patients with PHN in a pain clinic sample had visited their general physicians an average of 19 times (range 0 to 69 visits).[25]

2. Evaluating the Postherpetic Neuralgia Patient

A complete history and physical examination continue to be the standard for making the diagnosis of PHN. Pain is typically localised to the dermatome affected by the rash and most often described as burning, throbbing, or sharp and shooting in nature. Allodynia, the presence of pain in response to a normally innocuous stimulus, is common in PHN and often causes patients great distress. On examination there may be areas of scarring or hypopigmentation. With respect to pain quality and sensory findings, there appears to be more than one presentation characteristic of patients with PHN. Some have marked allodynia with minimal sensory deficits, and others may have marked sensory loss in the area of greatest pain with little or no allodynia. It has been suggested that these different patterns of findings may be used to guide treatment.[27]

3. Physical Treatments

Because allodynia is common in PHN, decreased stimulation to the periphery may be valuable in reducing symptoms. Natural fibre clothing is preferable to artificial fibres. A protective layer between the skin and provoking stimuli may be helpful; cling film, cut to size and shape, or a layer of 'plastic skin' may be applied intermittently. Transcutaneous electrical nerve stimulation (TENS) is occasionally helpful in established PHN,[28] but one study reported no benefit in a series of 17 patients.[29] Ultrasound has a poor record in a few small series of patients with PHN,[30,31] and acupuncture seems to provide little benefit in PHN,[32] although early treatment may be more effective.[33] Cold pack application often provides short term relief and is always worth trying, and a small pack of frozen peas is ideal because it can be moulded to the needed shape.

4. Pharmacological Approaches

Many different classes of medication have been used in the treatment of PHN. Unfortunately, most therapeutic options had not, until recently, been eval-

uated by accepted standards, i.e. randomised, double-blind, placebo-controlled trials. However, there is now a rapidly growing number of carefully designed and conducted studies being reported that examine the treatment of PHN.

4.1 Topical Agents

Capsaicin continues to play a minor role in the treatment of patients with PHN. Compliance with this treatment is low because of the intense burning after application, which may, however, lessen with time. The mechanism of action of capsaicin is unknown; hypotheses include a peripheral action through depletion of substance P in selective C fibres or perhaps central migration. There are two systematic reviews examining the use of capsaicin for PHN. Volmink et al.[34] reported that the 0.075% preparation of capsaicin provides a statistically significant benefit, whereas McQuay and Moore[35] found that there was no evidence of significant improvement following capsaicin treatment in patients with PHN. In some countries, a 0.025% preparation of capsaicin has recently become available; initial experience suggests that some patients find this preparation helpful and that it may be better tolerated. Placebo-controlled studies of capsaicin are problematic because of the difficulty in blinding caused by the burning associated with active treatment.

Nonsteroidal anti-inflammatory drug (NSAID) creams have been investigated in several studies and may help some patients with PHN, although the evidence is inconclusive.[36-38] Limited studies of aspirin suspended in chloroform, ether or acetone have been reported.[39-42] There is doubt regarding the extent of clinical benefit of this treatment, and concern regarding the safety and stability of the mixtures. It is one of many therapies that helps some patients.

Various local anaesthetic preparations may be applied to allodynic skin, including lidocaine and EMLA (eutectic mixture of local anaesthetics, prilocaine and lidocaine). They may be adsorbed onto various dressing materials, applied under occlusive dressings, or administered by iontophoresis. Most publications suggest that these treatments may have value, but often this conclusion has been based on case reports or uncontrolled series of patients.[43-45]

Rowbotham and colleagues have recently presented the results of several double-blind vehicle-controlled studies in which topical lidocaine in either gel or patch form relieved pain in patients with PHN with allodynia.[46-48] A majority of patients treated with the lidocaine patch have reported moderate or greater pain relief. On the basis of the results of these studies, the US Food and Drug Administration recently approved a lidocaine patch (Lidoderm™)[1] for the treatment of PHN. There is minimal systemic uptake and no need for dose escalation with use of the lidocaine patch. These qualities make this treatment approach a very desirable alternative from the perspective of physicians (minimal concern about contraindications and drug interactions) as well as patients (relatively rapid onset of relief).

4.2 Oral Medications

4.2.1 Antidepressants

Tricyclic antidepressants (TCAs) have been the first-line treatment for patients with PHN since demonstrations in randomised controlled trials that these medications have an analgesic effect in chronic neuropathic pain that is independent of their antidepressant effect. There have been several reviews of studies of the efficacy of antidepressants in the treatment of various neuropathic pain syndromes, and an overview of the studies of TCAs in PHN[7,49-54] is presented in table I. Volmink et al.[34] calculated estimates of efficacy expressed in odds ratios and concluded that both amitriptyline and desipramine are effective in relieving PHN pain. McQuay et al.,[55] on the basis of number needed to treat analyses, reported that amitriptyline and desipramine are significantly better than both placebo and lorazepam in the treatment of PHN. An apt summary of the literature on antidepressants and neuropathic pain is provided by the title of a recent article by Max,[56] '[t]hirteen consecutive well-designed ran-

1 Use of tradename is for product identification only and does not imply endorsement.

Table I. Summary of controlled trials of antidepressants in postherpetic neuralgia (modified from Max[49])

Reference	Drug	No. of patients	Response (%)
Watson et al.[50]	Amitriptyline	24	67
	Placebo		5
Max et al.[7]	Amitriptyline	34	47
	Placebo		8
Kishore-Kumar et al.[51]	Desipramine	19	63
	Placebo	11	11
Watson and Evans[52]	Amitriptyline	15	60
	Zimeldine (zimelidine)		7
Watson et al.[53]	Amitriptyline	32	44
	Maprotiline		18
Watson et al.[54]	Amitriptyline	31	58
	Nortriptyline		55

domized trials show that antidepressants reduce pain in diabetic neuropathy and postherpetic neuralgia'.

Because the majority of studies of antidepressants in neuropathic pain have examined amitriptyline, it has been the most widely used antidepressant in the treatment of PHN. However, amitriptyline is one of the TCAs with the greatest number of adverse effects, including sedation, anticholinergic effects and postural hypotension. Although other TCAs, for example, desipramine and nortriptyline, have fewer of these adverse effects, it has been unclear whether the analgesic effects of these medications are equivalent to the well established efficacy of amitriptyline. To address this very important question, Watson et al.[54] conducted a double-blind crossover trial comparing amitriptyline and nortriptyline in a sample of patients with PHN. The results demonstrated that these two TCAs had equivalent analgesic effects in PHN but, as expected, nortriptyline was better tolerated by patients because of its more favourable adverse effect profile.

It has remained uncertain whether a dose-response relationship exists for treatment with antidepressants in patients with chronic pain or whether there is a therapeutic window below and above which pain control is suboptimal.[7,57-59] In the recent study comparing nortriptyline and amitriptyline,[54] only 4 patients out of 31 appeared to have an initial good response that worsened as the dosage was increased. The authors concluded that if a therapeutic window exists at all, it is most likely a rare phenomenon.

Although TCAs such as nortriptyline and desipramine are better tolerated than amitriptyline, the adverse effects of these medications continue to pose a limitation in the treatment of patients with PHN. Selective serotonin reuptake inhibitors (SSRIs) have fewer adverse effects than TCAs, but there are no placebo-controlled studies examining the effectiveness of SSRIs in the treatment of PHN. In studies of patients with painful diabetic neuropathy, paroxetine and citalopram were associated with significantly greater pain relief than placebo,[60,61] whereas fluoxetine was found to be no more effective than placebo.[62]

The newer antidepressant venlafaxine inhibits both noradrenaline and serotonin reuptake but lacks significant muscarinic adverse effects. Although venlafaxine has been shown to reduce thermal hyperalgesia in rats with experimentally produced neuropathic pain[63] and anecdotal reports suggest that it may have an analgesic effect in patients with neuropathic pain,[64] no controlled clinical trials of this antidepressant have been reported in patients with chronic pain.

4.2.2 Anticonvulsants

Carbamazepine and phenytoin have traditionally been used for the management of neuropathic pain and have a beneficial effect in trigeminal neuralgia and diabetic neuropathy.[35,65] Evidence for benefit in PHN is lacking and their adverse effects, particularly in the elderly and frail, can be unpleasant. Indeed, Watson[66] concluded that the benefit of treatment of PHN with anticonvulsants has often been unimpressive[67] or difficult to interpret because of concomitant use of antidepressants.[29,68,69]

Although a review of published studies of anticonvulsant drugs in patients with chronic pain suggested that there is no support for their use in PHN,[65] this conclusion must now be changed because of the results of the largest clinical trial conducted to date in PHN. In a double-blind study, Rowbotham et al.[70] randomised 229 patients with PHN to receive gabapentin or placebo for 8 weeks. Gabapen-

tin was titrated to a maximum dosage of 3600mg daily. Treatment with gabapentin was associated with a significant reduction in average daily pain ratings as well as improvements in sleep, mood and quality of life. The safety and efficacy of gabapentin treatment in patients with PHN appeared to be at least as favourable as that reported for antidepressant treatment. The adverse effects of gabapentin include somnolence and dizziness, but its generally excellent tolerability and high clearance rate distinguish it from other anticonvulsants. These characteristics and its efficacy in multiple domains of the chronic pain experience suggest that gabapentin should be considered a first-line treatment in patients with PHN, especially those without depressive symptoms requiring antidepressant treatment.

4.2.3 Analgesics

Oral NSAIDs seem to be of little benefit in acute herpes zoster pain or in PHN,[71] although paracetamol combined with weak opioids is often prescribed. For many years, it has been argued that neuropathic pain is unresponsive to opioid medications. Recent intravenous[72] and nonblind[73] studies have suggested that patients with PHN can obtain significant pain relief from opioid analgesics, and these medications have become more widely used in the treatment of PHN and other neuropathic pain syndromes.

Watson and Babul[74] recently published a placebo-controlled crossover trial of 38 patients with PHN receiving an average of 45mg (range 20 to 60mg) of controlled release oxycodone. Patients treated with oxycodone had significantly greater pain relief, reduction of allodynia, decreased disability, and patient preference than patients receiving placebo. These results not only establish that opioid analgesics have an important role in the treatment of PHN; they also provide compelling evidence that neuropathic pain responds to opioids.

Another analgesic with recently demonstrated efficacy in neuropathic pain is tramadol, a weak opioid μ-receptor agonist and monoamine (i.e. noradrenaline and serotonin) reuptake inhibitor.[75] In a pilot study of patients with PHN, tramadol was compared with clomipramine alone and combined with levomepromazine; 9 of 10 patients in the tramadol group reported their pain relief was satisfactory or better.[76] Controlled evidence of the analgesic effect of tramadol in neuropathic pain is provided by a double-blind study of painful diabetic neuropathy in 131 patients in which an average dosage of tramadol 210mg daily was significantly better than placebo in reducing pain and in improving physical and social functioning.[77]

4.2.4 Ketamine and NMDA Receptor Antagonists

The *N*-methyl-D-aspartate (NMDA) receptor is complex and involved in peripheral and central pain pathways, although little is known of peripheral effects in clinical pain. Centrally acting drugs are available, albeit with unwanted adverse effects, which include ataxia, somnolence, short term memory loss and other psychological symptoms. In central sensitisation states, it is possible that potentiation of opioid analgesics may be a useful benefit of NMDA receptor antagonists. An indirect effect on the receptor may be achieved by agents acting at the glycine site.

NMDA receptors are involved in the development and maintenance of changes in neuronal excitability that are relevant to the development of sensitisation, allodynia and the persistence of pain following neural damage. Ketamine is known to produce analgesia at least partially as a result of blocking these receptors. Recent studies have shown that ketamine reduces pain in some patients with PHN,[78-80] but with adverse effects and possibly other complications of ongoing use.[81] Based on these initial reports, increasing attention is being paid to the role of NMDA antagonists in the treatment of neuropathic pain, with the challenge being to find agents with a more favourable therapeutic ratio than ketamine.

Dextromethorphan (an antitussive) is an NMDA receptor antagonist that appears to have an analgesic effect, but there is limited evidence of its efficacy, especially in neuropathic pain. Dextromethorphan in relatively low doses, for example, 20mg three times daily, has not produced lasting analgesia and may be rejected because of adverse effects.[82] In a recent double-blind, placebo-controlled trial,

dextromethorphan was titrated to mean dosages of 439 mg/day in 13 patients with PHN and to 381 mg/day in 13 patients with painful diabetic neuropathy.[83] There was evidence of a statistically significant beneficial effect of dextromethorphan treatment in the patients with diabetic neuropathy, but not in those with PHN. The role of NMDA receptor antagonists in the treatment of PHN needs to be clarified by the results of future studies of dextromethorphan and other NMDA antagonists, such as memantine and amantadine.[84,85] Because methadone both blocks the NMDA receptor and is a long-acting opioid analgesic, it would also be valuable to examine whether this agent may have a unique role to play in the management of PHN and other neuropathic pain syndromes.

4.2.5 Other Drugs

There is a long list of drugs supported by publications varying from single case reports to uncontrolled studies. Although many of these drugs may provide relief in a few patients with PHN, the natural history of herpes zoster pain, placebo effects, and regression to the mean must be considered in any evaluation of their effectiveness.[86] A very partial list of drugs that have been used in the treatment of herpes zoster pain includes iontophoresis with vincristine,[87] calcium antagonists,[88] and lidocaine.[72] Lidocaine administered intravenously was shown to produce pain relief in patients with PHN equivalent to that of morphine and superior to placebo, although the mechanism of action is unclear.[72] This analgesic effect of systemic lidocaine may occasionally be reproduced by oral mexiletine or flecainide. However, these drugs are often rejected by patients because of adverse effects.

4.3 Nerve Blocks

Interpleural nerve blocks have been used for both acute herpes zoster pain and PHN.[89-91] Subcutaneous injections of local anaesthetics may produce a temporary reduction of allodynia and hyperpathia (a painful syndrome characterised by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold). It is possible that this effect is prolonged by the addition of depot steroid, and 'pain holidays' may be cautiously offered for such events as weddings to patients in whom a few days of symptom relief follows these injections. Peripheral blocks may reduce allodynia but whether the temporary effects of a local anaesthetic block can be prolonged by neurolysis, be it chemical, heat or cold induced, remains uncertain. Abolition of sensory input by nerve destruction may, at times, lead to increased pain resulting from deafferentation.

Sympathetic nerve blocks have often been reported to be effective in relieving acute pain in herpes zoster, and it has been proposed that they may have a role in the prevention of PHN.[92,93] Based on a review of 77 patients with PHN, it was reported that stellate ganglion blocks provided 'good' pain relief in 50% of patients who had pain for less than 1 year but in only 25% of patients who had pain for more than 1 year.[94] Similar data have also been presented by Winnie and Hartwell,[95] comparing sympathetic nerve blocks done within 2 months of the onset of herpes zoster infection with blocks done more than 2 months after onset. Unfortunately, both of these studies were uncontrolled, making it impossible to distinguish greater efficacy of earlier treatment from the natural history of pain resolution in herpes zoster and PHN.[96]

Dan, Higa and colleagues[97-99] have reported that repeated sympathetic nerve blocks and continuous epidural infusions shorten the duration of acute herpes zoster pain and thereby reduce the development of PHN. Unfortunately, the intensity of the treatment described by these investigators – for example, a mean of 153 sympathetic nerve blocks for inpatients and 20 blocks for outpatients, with 36% of patients being treated as inpatients[97] – is impractical in most medical settings. In addition, because limited data have as yet been provided on the follow-up of these patients, little is known regarding possible recurrences of pain and long term complications of treatment.

Intrathecal and epidural injections of long-acting corticosteroids were compared in patients with 'intractable' PHN (more than 1 year in duration) in a recent study.[100] The results suggested that methyl-

prednisolone acetate injected weekly for 4 weeks significantly reduced allodynia and continuous and lancinating pain in the intrathecal group, and that these effects were greater in this group than in the epidural group. The risks of intrathecal steroids are well documented in the literature and include neurological complications and adhesive arachnoiditis.[101] It will be important to know the long term outcome of the patients in this study with respect to both pain relief and adverse events.

5. Psychosocial Interventions

Elderly patients are often lonely, and adverse major life events such as bereavement and loss of independence are common. They may have pre-existing anxiety or depression, or may develop such changes secondary to a severe acute herpes zoster infection and the development of prolonged pain.[102-104] As in every other chronic pain syndrome, such factors should be carefully evaluated in patients with PHN. Providing the patient with an understanding of the disease as well as recommending an appropriate level of social activity are frequently helpful. As with all chronic pain syndromes, an individual management strategy should be developed for each patient. Thomsen's book[105] makes helpful reading for thoughtful patients with PHN.

Cognitive-behavioural therapy, including such specific interventions as relaxation training, biofeedback and hypnosis, has a well established role in the treatment of patients with chronic pain.[106,107] Although no studies have been reported that have specifically examined this form of treatment in patients with PHN, there is no reason to doubt that cognitive-behavioural therapy provides as significant a benefit in PHN as it does in all of the other chronic pain syndromes in which it has been studied.

6. Neuroinvasive Measures

Loeser[108] has provided a comprehensive review of a large number of surgical procedures that have been used for the treatment of PHN, including skin excision, sympathectomy, dorsal root entry zone lesions, cordotomy, thalamotomy, cingulumotomy, and spinal cord and deep brain stimulation. The studies describing the results of treating patients with PHN with these procedures have invariably examined small numbers of patients. None of these studies have been controlled, and the duration of patient follow-up has often been inadequate. Although some surgical procedures may provide significant relief for a small number of patients with PHN, these procedures are not without risk and are seldom recommended for the treatment of PHN. Moreover, the role for these procedures will undoubtedly diminish as the number of efficacious pharmacological treatments for PHN increases.

7. Pain Management Centres

Pain clinics specialise in the treatment of patients who suffer from pain syndromes such as chronic low back pain. These centres offer patients a multidisciplinary treatment programme that usually includes some form of cognitive-behavioural therapy. The goals of such multidisciplinary treatment are not only to reduce pain to the greatest extent possible but also to improve function (i.e. reduce disability), decrease psychological distress, and increase quality of life. These latter goals are often more realistic than pain reduction, especially in the large percentage of patients who arrive at pain clinics after having failed to respond to several different treatment approaches. For this reason, the reduction of pain intensity is not considered the primary goal in many pain management centres. However, pain reduction may occur in these settings, either as a result of the medical treatments provided or because cognitive-behavioural therapy has reduced suffering and psychological distress and increased the patient's ability to cope effectively with prolonged pain. These programmes are appropriate for patients with PHN but must take into account the fact that many of these patients are elderly and return to work is not a relevant goal. In our view, a contingency to improve quality of life is mandatory for patients in whom inadequate pain relief is common.

8. Toward a Treatment Algorithm

Various algorithms have been presented for the treatment of acute herpes zoster and PHN (see Kost and Straus[1] for a recent example). In the past year, there have been 4 major advances in our understanding of the treatment of PHN that have resulted from randomised, controlled trials discussed above. These major advances are the demonstrations that gabapentin, sustained release oxycodone and the topical lidocaine patch are efficacious in patients with PHN, as well as the report that nortriptyline and amitriptyline provide equivalent analgesic benefits in PHN but that nortriptyline is better tolerated. Because these advances in the treatment of PHN are so recent, it seems premature to suggest a specific treatment algorithm for PHN. One of these treatment approaches is only just becoming commercially available (i.e. the lidocaine patch), and so clinical experience is lacking. In addition, there are no data regarding the percentages of patients who do not respond to one of these treatments (e.g. nortriptyline) but who then go on to obtain satisfactory pain relief from another (e.g. gabapentin). Furthermore, it is important to recognise that there are no data on the efficacy of combinations of these treatments when compared with monotherapy.

Although we will not present a treatment algorithm, we would like to propose a treatment approach for PHN (considering it any pain persisting at least 3 months after rash onset) that takes into account these recent advances. Our approach assumes that the patient has had a comprehensive history taken and a physical examination, and has received a careful explanation of the disease and the proposed treatment plan. Encouragement, reassurance and advice on quality of life matters are also important, and include supporting early return to premorbid activity levels and recommendations regarding massage, clothing, cold packs and the use of cling film.

Within the context of this supportive doctor-patient relationship, the lidocaine patch, a tricyclic antidepressant or gabapentin are the options for initial treatment of a patient with PHN. In patients with significant allodynia, the lidocaine patch provides a treatment approach that is likely to be well tolerated and offer considerable benefit.[48] Importantly, whether the patient obtains satisfactory relief from the lidocaine patch will usually be apparent within a week (or 2 at the most) because time-consuming dose escalation is not required.

Based on the results of the Watson et al. study,[54] nortriptyline can be considered the preferred TCA for the treatment of PHN. It is imperative that a clear explanation of the rationale for treatment be given, that is, that antidepressants have an analgesic effect independent of their antidepressant effect. It is best to start TCAs at low doses – nortriptyline 10 to 20mg at bedtime – especially in elderly patients, and to then increase the dosage to a level that produces acceptable pain relief or unacceptable adverse effects. The dosage may be titrated as tolerated to nortriptyline 150 mg/day before considering the patient a nonresponder. Desipramine may be used if the patient experiences unacceptable sedation from nortriptyline; morning administration may be required because some patients experience insomnia when desipramine is given at bedtime.

As with TCAs, treatment with gabapentin should be initiated at low dosages (e.g. 100 to 300mg three times daily), and then escalated as tolerated to 3600 mg/day, the final dosage examined in the placebo-controlled trial,[70] provided there is no reason to believe that the patient has renal insufficiency. Gabapentin appears to be 'at least as effective as TCAs, at least as safe, and with fewer contraindications to use'.[70]

The efficacy of sustained release oxycodone up to dosages of 30mg twice daily has also been demonstrated. Watson and Babul[74] noted that the magnitude of the analgesic effect was 'at least comparable to that provided by tricyclic antidepressants'. Adverse effects such as constipation, sedation and nausea were associated with oxycodone treatment, but the latter two diminish with therapy. Despite these adverse effects, 67% of 38 patients preferred oxycodone at the conclusion of this blinded crossover trial (versus 11% who preferred placebo). The results of this study suggest that sustained release

opioid analgesics should be considered earlier in the treatment of patients with PHN than has been customary.

These four treatments for PHN, the lidocaine patch, TCAs, gabapentin and oxycodone, provide the clinician with an evidence-based approach for treating PHN that was not available until very recently. Unfortunately, all of the research studies that demonstrated their efficacy examined these treatments only as single agent therapy; as yet, no studies have been reported that examine these treatments in the various possible combinations. Despite this lack of controlled data, many clinicians will want to consider using combinations of these four treatments, when patients fail to respond to a single agent or even at the beginning of treatment to increase the likelihood of a beneficial response.

In treating patients with PHN, it is essential to undertake frequent review of treatment compliance, analgesic effects, and adverse effects of these medications until stability of dosage is achieved. In many patients, this can be managed by regular telephone contacts. It can be expected that some patients will not respond to these four treatments, although the percentage of such patients is not known at present. For these unfortunate patients, there are a large number of alternative treatments discussed above that deserve consideration. These include tramadol, SSRIs (especially paroxetine and citalopram), other anticonvulsants, TENS, capsaicin, lidocaine infusion followed by oral mexiletine, and nerve blocks. For many patients who do not respond to the first-line treatments, referral to a pain management centre should also be considered, sooner rather than later. Even if early pain clinic treatment is no more efficacious than later treatment, the suffering and disability caused by PHN provide a compelling argument for doing everything that can be done to help the patient as quickly as possible.

One issue we have not addressed is the relative costs of the different treatment approaches available for patients with PHN. Depending on the country or region and the patient's medical benefits, pharmacoeconomic considerations may play a large role in treatment decisions. Because of the enormous geographic variation in the costs and availability of the different treatments we have discussed, the only general guideline we can recommend is that clinicians become as familiar as possible with these considerations. Doing so will not only benefit the financial welfare of patients, but also maximise the likelihood that patients will comply with treatment.

9. Preventing Postherpetic Neuralgia

An important goal for future research is the development of even more effective treatments for PHN. However, even though better treatments are needed, it has become clear that the prevention of PHN may also be an effective strategy.[109-111] A method for preventing PHN before it starts would not only make the development of more effective treatments unnecessary but would also eliminate the disability, psychological distress and increased healthcare utilisation that are caused by PHN.

At present, antiviral drugs provide the greatest opportunity for reducing the likelihood that a patient with acute herpes zoster will develop PHN.[12-16] Nevertheless, a substantial number of patients with herpes zoster still have prolonged pain despite adequate antiviral therapy. Although it is possible that new antivirals with greater efficacy will be developed, a different strategy for preventing PHN is to supplement antiviral treatment in patients with acute herpes zoster. The appropriate design in research on the prevention of PHN is to compare an antiviral agent combined with an investigational treatment versus an antiviral agent combined with a placebo matching the investigational treatment, as has been done in recent studies of the effects of corticosteroid treatment in patients with acute herpes zoster.[112,113] There are a variety of drugs with demonstrated efficacy in PHN and/or painful diabetic neuropathy that could be evaluated in patients with acute herpes zoster, including TCAs, gabapentin, oxycodone and tramadol.[111,114,115] It would also be extremely worthwhile to undertake a similarly designed controlled study to determine whether nerve blocks during acute herpes zoster augment

the efficacy of antiviral agents in preventing PHN.[93] In research on the prevention of PHN, it is essential to begin treatment as soon as possible after rash onset, regardless of whether the goal is to limit nerve damage, reduce central sensitisation, or attenuate acute pain. Such studies will make it possible to determine whether PHN can be prevented more successfully than it is currently treated.

10. Conclusions

There are several reasons why the number of patients experiencing PHN may increase substantially in the future. Firstly, the results of a recent epidemiological study suggested that the incidence of herpes zoster has increased in recent decades, although the explanation for this was unclear.[116] In addition, the incidence of herpes zoster may be expected to increase in coming decades, not only as the number of older individuals in the population increases but also as a result of the increasing prevalence of immunosuppression associated with various diseases and medical treatments.[117] Finally, because PHN is more likely to develop in older individuals, it can be expected to become more prevalent as the population ages.[118]

Until recently, this epidemiological forecast was a cause for major concern. Even though a variety of approaches have been available for the treatment of PHN, a large percentage of patients either failed to respond or derived only partial benefit and continued to be in pain for months or even years. A substantial increase in the prevalence of PHN would therefore have major public health implications. However, it is clear that the major advances in the treatment of PHN made in the past 2 years provide a basis for great optimism for the future. The pharmaceutical industry considers PHN a model neuropathic pain syndrome for examining the efficacy of emerging analgesics. Hence, there is every reason to expect continued major advances in the successful treatment of patients with this chronic pain syndrome.

Another reason for optimism involves ongoing research on the prevention of herpes zoster, and therefore PHN, by administration of the varicella vaccine. In preliminary studies, administration of this live attenuated vaccine increased varicella zoster virus-specific cell-mediated immunity to levels comparable to those found in individuals with a history of zoster and may also have attenuated the development of herpes zoster.[119-121] On the basis of these data, large-scale placebo-controlled trials are being conducted to evaluate the impact on herpes zoster and PHN of administering the varicella vaccine to older adults. If the results of these clinical trials demonstrate that the varicella vaccine markedly attenuates herpes zoster and its use then becomes widespread, PHN may become so rare that it ceases to be a feared complication of herpes zoster.

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