



# Recommendations for the Management of Postherpetic Neuralgia

## Multidisciplinary Panel on Neuropathic Pain\*

**T**hese recommendations from the Multidisciplinary Panel on Neuropathic Pain provide an update of the recommendations first published in 2003.<sup>1</sup> The current recommendations include new data on pharmacological and nonpharmacological strategies for the management of postherpetic neuralgia (PHN).

The Recommendations for the Management of Postherpetic Neuralgia are the product of review and appraisal of current evidence in the medical literature. The

recommendations serve to assist healthcare professionals in evaluating a patient's condition and deciding on a suitable treatment modality. They are not intended to replace professional judgment in determining the appropriate management of individual patients. While we have taken due care in preparing the recommendations, we cannot warrant the accuracy of the original publications. In selecting good-quality references, a certain degree of judgment based on our professional knowledge in the subject was needed. Such

### \*Panel members:

**Chen Phoon Ping**, MBBS, FANZCA, FFPANZCA, FHKCA, FHKAM, DipPainMgt  
Consultant & Chief of Service, Department of Anaesthesiology & Operating Services, Alice Ho Miu Ling Nethersole Hospital & North District Hospital, Hong Kong SAR.

**Josephine WY Ip**, MBBS, MS, FRCS(Ed), FHKAM(Ortho), DipHandSurg(FESSH)  
Chief, Division of Hand and Foot Surgery, Department of Orthopaedic Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR.

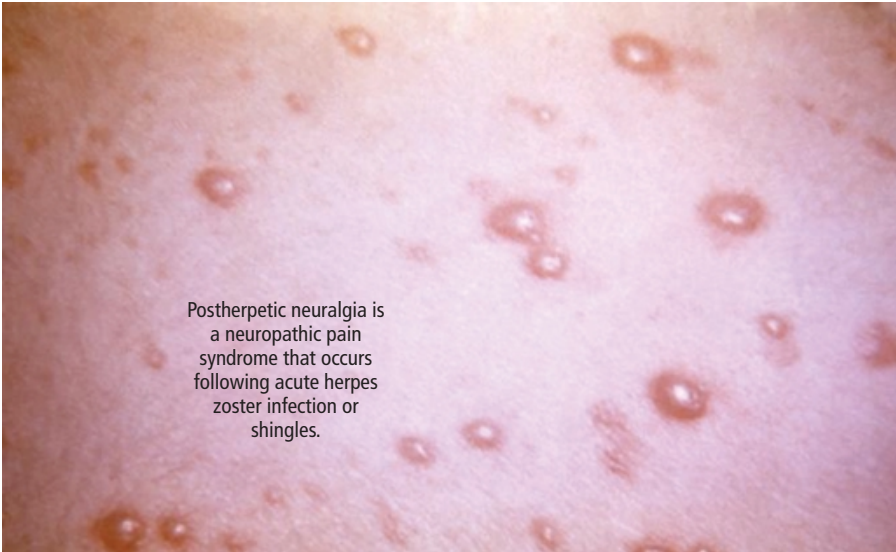
**Joseph MK Lam**, MBChB, FRCS(Edin), FCSHK, FHKAM(Surg)  
Consultant Neurosurgeon and Adjunct Associate Professor, Division of Neurosurgery, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR.

**Tsoi Tak Hong**, MBBS, MRCP, FRCP(Edin), FRCP(Glas), FHKCP, FHKAM(Med)  
Specialist in Neurology and Consultant Physician, Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong SAR.

**Wong Chun Por**, MBBS, FHKAM(Med), FRCP(Lond), FRCP(Glas)  
Chief of Service, Integrated Medicine Service, Consultant Geriatrician, and Head, Department of Geriatrics, Ruttonjee Hospital, Hong Kong SAR.

**Lawrence KS Wong**, MBBS, MD, MRCP, FHKAM(Med), FRCP  
Associate Professor, Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR.

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Postherpetic neuralgia is a neuropathic pain syndrome that occurs following acute herpes zoster infection or shingles.

Photo courtesy of CDC/ Dr. K.L. Hermann

biases are minimized by multidisciplinary discussion and review.

### I. Pathophysiology and Prevalence

PHN is a neuropathic pain syndrome that occurs following acute herpes zoster infection or shingles. Herpes zoster infection is caused by reactivation of the chicken pox virus (varicella zoster) that can lie dormant in the sensory nerve roots of the spinal cord. Virus reactivation may be associated with waning cellular immunity, caused either by age-related immune system dysfunction or immunosuppression.<sup>2</sup> Herpes zoster lesions typically erupt in the thoracic, cervical and ophthalmic dermatomes. Varicella zoster or chicken pox virus can damage all parts of the primary sensory neuron, including the dorsal root ganglion, which can lead to PHN. Both peripheral and central pathophysiological mechanisms have been identified or proposed.

PHN is usually defined as pain persisting for *more than 3 months* after the herpes zoster skin lesions

have healed. PHN is often difficult to treat and may last many years. As a consequence of PHN, patients may develop physical and social disabilities, as well as psychological distress.<sup>3,4</sup>

The reported incidence of PHN after acute herpes zoster infection varies from 9% to 34%.<sup>5</sup> PHN is uncommon in patients younger than 40 years, but the risk increases sharply with age; up to 75% of patients older than 70 years experience pain 1 month after healing, while 50% continue to have pain at 1 year.<sup>6,7</sup>

The following are risk factors for PHN<sup>2,5,7</sup>:

- old age;
- severe, acute pain during acute herpes zoster infection;
- severe skin eruption or rash during acute herpes zoster infection;
- sensory dysfunction in the affected dermatome during acute herpes zoster infection; and
- painful prodrome preceding the rash.

Antiviral treatment of acute herpes zoster infection (with famciclovir, valacyclovir or acyclovir)

may reduce the overall duration of pain and risk of developing PHN.<sup>8,9</sup> Corticosteroids have been used prophylactically by some clinicians, but there is little evidence to support their use. Good clinical evidence also suggests that prophylactic treatment with low-dose amitriptyline in patients older than 60 years reduces the prevalence of PHN by more than 50%.<sup>10</sup>

### II. Diagnosis

PHN is diagnosed on the findings of a complete medical history and physical examination. The diagnostic clinical features of PHN are:

- pain localized to the dermatome affected by the herpes zoster rash;
- pain described as burning and/or throbbing, or sharp and shooting;
- allodynia;
- pain accompanying movement;
- areas of scarring or hypopigmentation caused by the herpes zoster rash; and
- presence of psychosocial distress.

Patients with PHN can present with different symptom patterns. Some patients have marked allodynia with minimal sensory deficits, while others have minimal allodynia but substantial sensory loss. The pathological mechanisms behind these changes can be very complex, and several approaches are often needed to manage PHN successfully.

### III. Recommended Management of PHN

The mainstay treatments for PHN include tricyclic antidepressants (TCAs) and anticonvulsants.<sup>11-14</sup> Topical lidocaine, administered via a patch, also effectively treats PHN and provides an alternative choice

for patients who experience systemic side effects with other therapies.<sup>15-17</sup> In addition, recent evidence suggests a possible role for oral opioid analgesics in the management of PHN.<sup>18</sup> Physical therapy (eg, transcutaneous electrical nerve stimulation [TENS]) may be a useful adjunct, although there is no strong evidence for its effectiveness in PHN.

Patients remaining unresponsive to first-line therapies after 8 weeks should be referred to a pain medicine specialist. For these patients, a multidisciplinary approach to treatment is often appropriate.

Full details on pharmacological and nonpharmacological management of PHN are provided in Section IV of these recommendations.

### General Management

1. Conduct a careful medical and psychosocial evaluation.
2. Set a realistic expectation for the treatment.
3. Educate the patient on the disease and treatment side effects.
4. Provide psychosocial counselling, if necessary, taking into account the chronic nature of this pain syndrome. Counselling is intended to reduce influencing psychosocial factors that may affect the pain and to prevent the development of pain behaviours.

### Specific PHN Treatments

1. Start low-dose amitriptyline or nortriptyline therapy (10 to 25 mg at night) and titrate weekly up to the maximum tolerated dose or a maximum of 150 mg.
2. For patients older than 60 years, or in cases where TCAs are not tolerated or are contraindicated, gabapentin may be used. In some practices, gabapentin is

considered first-line therapy for PHN. Pregabalin is emerging as an effective alternative.

3. Add a topical local anaesthetic, such as a lidocaine patch or EMLA (eutectic mixture of local anaesthetic) cream. This can be first-line treatment if antidepressants and anticonvulsants are contraindicated.
4. Carbamazepine is commonly used to treat PHN, but there is little evidence to support its use in this neuropathic pain condition.
5. Consider tramadol or opioids if antidepressants and anticonvulsants are ineffective or are contraindicated.
6. Consider TENS as adjunctive therapy.
7. If adequate pain control is not achieved after 8 weeks, consider referring the patient to a pain medicine specialist for alternative therapies, such as N-methyl D-aspartate (NMDA) receptor antagonists, intrathecal steroids, intravenous adenosine 5'-triphosphate (ATP), or combination therapy. A multidisciplinary approach to managing these difficult-to-treat patients may be necessary.

## IV. Pharmacological and Nonpharmacological Management of PHN

The pharmacological treatments included in these recommendations are based on published clinical evidence in PHN patients and current clinical practice. However, some agents may not be approved for use in neuropathic pain syndromes. Full prescribing information should be consulted before initiating drug therapy.

### Pharmacological Treatment

#### TCAs

TCAs block noradrenaline and serotonin reuptake, and may relieve pain by increasing the inhibition of spinal neurons involved in pain perception. Many randomized trials have demonstrated the efficacy of TCAs in PHN, and several comprehensive reviews have been performed.

One systematic review of randomized trials for PHN treatments reported TCAs, particularly amitriptyline and desipramine, as the only effective treatments available.<sup>5</sup> In five trials of TCAs, four of which evaluated amitriptyline and one desipramine, 47% to 67% of patients received moderate to excellent pain relief.<sup>2</sup> Another review showed that, in two out of three PHN studies, the combined odds ratio for TCAs in PHN was 6.8 and the number-needed-to-treat (NNT) to obtain 50% pain relief in one patient was 2.3.<sup>11</sup> Pooling of three placebo-controlled trials using TCAs for PHN (two trials with amitriptyline and one with desipramine) determined that the NNT for at least 50% pain relief was 2.1.<sup>12</sup>

The most widely used TCA for PHN is amitriptyline. However, being one of the oldest TCAs, it has significant adverse effects, including sedation, anticholinergic effects and postural hypotension. Nortriptyline has a more favourable adverse-effect profile and was as effective as amitriptyline in a double-blind, crossover trial of 33 patients.<sup>19</sup> Desipramine is an effective alternative for patients who cannot tolerate amitriptyline, although the two TCAs have not been directly compared in a randomized trial.

Early drug initiation can improve the success of therapy with TCAs.

A retrospective study found that the time at which TCA therapy is commenced is the most predictive factor of treatment outcome.<sup>20</sup> Two thirds of patients are expected to achieve pain relief (NNT=1.8) when TCAs are initiated 3 to 12 months after acute herpes zoster infection, compared with one third (NNT=8.3) when TCAs are commenced more than 2 years after the herpes zoster episode.

#### Dosing Schedule for TCAs

TCAs are contraindicated in patients with recent myocardial infarction, arrhythmia and severe liver disease. However, tolerance to their side effects can develop, so patients should be encouraged to persist with therapy. Side effects are reduced if low doses are used initially and increased gradually. Therefore, it is recommended to start amitriptyline at 10 to 25 mg daily at bedtime and increase slowly over 2 to 3 weeks to 150 mg daily. For nortriptyline, start at 10 to 20 mg at bedtime and increase as tolerated to 150 mg/day. Patients should only be considered unresponsive to treatment if they have failed to respond to either of these regimens. Desipramine may be used if patients experience unacceptable sedation from nortriptyline.

If pain relief is not achieved after 8 weeks on TCA therapy, then the patient should be referred to a specialist pain centre for further management.

#### Other Antidepressants

There is no evidence to support the use of lorazepam<sup>2,7</sup> or selective serotonin reuptake inhibitors (SSRIs)<sup>2,7,12</sup> in PHN. Furthermore, the efficacy of venlafaxine has yet to be evaluated in a controlled clinical trial.<sup>7</sup>

#### Anticonvulsants

Evidence from two large, placebo-controlled, randomized trials indicated that gabapentin is a useful alternative to amitriptyline.<sup>13,14</sup> Although carbamazepine has been used for managing neuropathic pain and is effective in treating trigeminal neuralgia and diabetic neuropathy, there is no evidence to indicate its effectiveness in PHN. Despite this, it is often used to treat PHN patients; consider carbamazepine if gabapentin and TCAs are not tolerated. Commence carbamazepine at 100 to 200 mg daily, with a maximum dose of 1,200 mg/day.

A multicentre, randomized, double-blind, placebo-controlled study evaluated gabapentin (1,800 mg and 2,400 mg) in 334 patients with defined PHN.<sup>13</sup> This trial reported significant reductions in pain scores, starting from week 1 of treatment, for both doses of gabapentin compared with placebo. Sleep quality and some domains of the SF-36 quality-of-life questionnaire also improved significantly with gabapentin treatment. Overall, gabapentin was well tolerated, with dizziness and somnolence being the most common adverse events.<sup>13</sup> Another randomized, placebo-controlled trial of 229 patients with PHN reported similar results with gabapentin (up to 3,600 mg/day). Treatment with gabapentin significantly reduced pain and sleep interference, and improved measures of mood and quality of life.<sup>14</sup>

More recently, a double-blind, randomized, placebo-controlled trial evaluated gabapentin (up to 2,400 mg/day) in patients with a variety of neuropathic pain syndromes, including PHN (14% of patients).<sup>21</sup> Gabapentin reduced pain and improved some quality-of-life

measures in patients with neuropathic pain syndromes.

These trials provide good evidence for the efficacy and safety of gabapentin. With fewer side effects than TCAs and a lack of drug interactions<sup>22</sup>, gabapentin is suitable as first-line medication in PHN and is particularly useful for elderly patients.

#### Dosing Schedule for Gabapentin

Gabapentin should be commenced as a single 300 mg dose on day 1 at bedtime and increased by 300 mg, every 3 days, up to a dose of 1,800 mg daily after 1 week (given in 3 divided doses).<sup>1</sup> If higher daily doses are required for maintenance, the maximum recommended dose is 3,600 mg daily (a lower dose is recommended in patients with renal impairment). For elderly patients or patients susceptible to side effects, it is recommended to increase the gabapentin dosage by 300 mg every week, or to commence with a lower dose (eg, 100 mg).<sup>1</sup> Patients should be referred for specialist management if pain relief is not achieved after 8 weeks' treatment with gabapentin.<sup>1</sup>

#### Other Anticonvulsants

Clinical trials have demonstrated that pregabalin, a novel anticonvulsant drug, is an effective treatment for neuropathic pain syndromes, including PHN. A 12-week, randomized, double-blind, multicentre, placebo-controlled, parallel-group study evaluated the efficacy of flexible (ie, weekly escalating dose up to 600 mg/day based on patients' responses and tolerability) and fixed (ie, 300 mg/day for 1 week then 600 mg/day for 11 weeks) pregabalin regimens in patients with chronic PHN or painful diabetic

peripheral neuropathy.<sup>23</sup> Compared with placebo, both flexible- and fixed-dose pregabalin regimens significantly reduced mean pain score ( $p=0.002$  and  $<0.001$ , respectively) and improved pain-related sleep interference ( $p<0.001$ ).

Moreover, a multicentre, parallel-group, double-blind, placebo-controlled, 8-week, randomized clinical trial on 173 patients with PHN showed pregabalin 300 or 600 mg/day (dose given depended on the patient's creatinine clearance) effectively reduced pain.<sup>24</sup> Pregabalin-treated patients had a greater decrease in the mean pain ratings at endpoint (over the last 7 days of treatment) compared with placebo (3.60 vs 5.29,  $p=0.0001$ ). Pregabalin also significantly reduced pain after the first full day of treatment and throughout the study. Trials also showed pregabalin was superior to placebo with regard to sleep, mental well-being and global improvement.<sup>24,25</sup> Pregabalin had acceptable tolerability compared with placebo, with side effects being generally mild to moderate.<sup>24</sup>

Oxcarbazepine may be another therapeutic option. Preliminary data from an open-label trial suggest that oxcarbazepine significantly reduced mean visual analogue scale (VAS) pain scores in patients unresponsive to carbamazepine and gabapentin ( $p<0.0001$ ).<sup>26</sup> Allodynia, patient functioning and quality of life also improved. These results have yet to be proven in randomized controlled trials.

For patients reporting shooting or lancinating pain, a trial of phenytoin, sodium valproate or carbamazepine may be beneficial, as some uncontrolled studies have reported these agents to be effective for this type of pain.<sup>2</sup>

#### *Topical Lidocaine Patch & EMLA*

Based on the results of three double-blind, vehicle-controlled studies using topical lidocaine (in a patch or gel) for patients with PHN, the US Food and Drug Administration approved a 5% lidocaine patch for PHN. The majority of patients in these trials experienced moderate or greater pain relief.<sup>15-17</sup> Patients treated with the patch had no systemic side effects and the patch was well tolerated when applied on allodynic skin for 12 hours. However, this lidocaine preparation is currently unavailable in Hong Kong.

EMLA cream is a eutectic mixture of the local anaesthetics prilocaine and lidocaine. In a small, uncontrolled trial, applying EMLA cream and leaving it under occlusive dressings for 5 hours a day was shown to reduce hyperalgesia.<sup>27</sup> Several case reports have also shown EMLA cream to be effective in PHN.<sup>28,29</sup> This preparation is relatively simple to apply and does not have any major side effects.

#### *Opioid Analgesics*

Neuropathic pain has generally been considered less responsive to opioid analgesics than nociceptive pain, but recent evidence shows some patients experience pain relief with these agents.<sup>2,7</sup> In a pilot study of patients with PHN, tramadol, a weak  $\mu$ -opioid receptor agonist and monoamine-reuptake inhibitor, was found to provide satisfactory pain relief.<sup>17</sup> A randomized, double-blind, placebo-controlled, parallel-group trial in 127 patients with PHN showed that those treated with sustained-release tramadol had greater pain relief than placebo-treated patients ( $p=0.017$ ).<sup>30</sup> Another randomized, controlled, crossover trial in 38 patients with PHN receiv-

ing a daily average of 45 mg of controlled-release oxycodone found that oxycodone-treated patients had significant reductions in pain, allodynia and overall disability at the end of a 4-week dose titration period.<sup>31</sup> However, oxycodone is not available in Hong Kong.

#### *Intrathecal Corticosteroids*

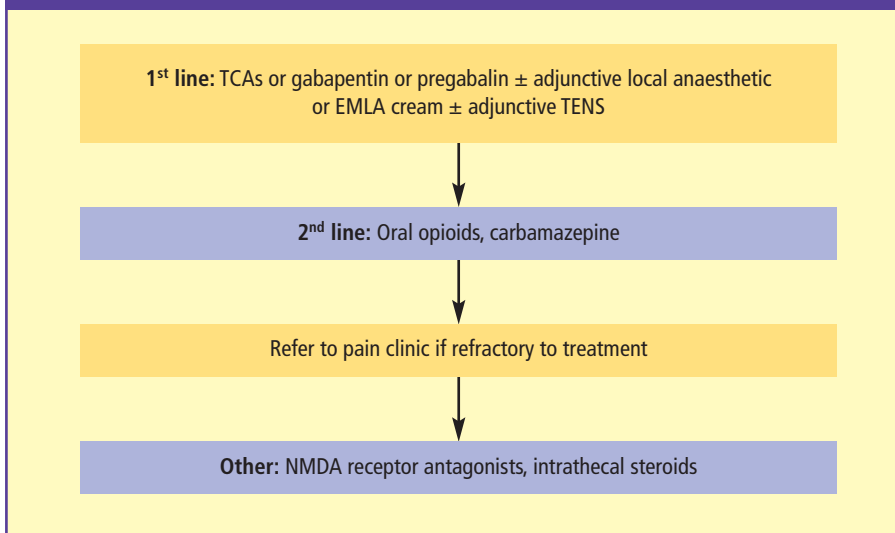
Intrathecal methylprednisolone and lidocaine was evaluated in a randomized, controlled trial, which showed that once-weekly administration for 4 weeks was effective for intractable PHN, reducing the pain intensity and area of allodynia by more than 70%.<sup>32</sup> Its effect was thought to be associated with the anti-inflammatory action of the drug. This was reflected by a change in the level of interleukin-8, a potent mediator of inflammation, in the cerebrospinal fluid after treatment.

#### *NMDA Receptor Antagonists*

These agents block the excitatory glutamate receptors in the central nervous system responsible for increased central sensitization following noxious stimuli. Currently available NMDA-blocking agents include ketamine, dextromethorphan, memantine and amantadine. The latter three agents may have a better safety profile than ketamine. Side effects of NMDA antagonists typically include sedation, nausea, psychological disturbances and hallucinations. Small cohort studies have shown ketamine to have an analgesic effect in patients with PHN.<sup>7</sup> Conversely, dextromethorphan is only effective in patients with diabetic neuropathy.<sup>7</sup>

#### *Intravenous ATP*

Activation of purinoceptors by ATP may improve neuropathic pain. An

**Figure. Proposed treatment algorithm for PHN**

open-label trial showed intravenous ATP 100 µg/kg/min for 120 minutes reduced VAS pain scores by more than 50% in 6 out of 12 PHN patients.<sup>33</sup> Pain relief developed slowly and lasted for a median of 9 hours. Ketamine-responsive patients were more likely to respond to ATP. Another open-label trial suggested that ATP 1 mg/kg infusion once weekly might improve spontaneous continuous pain, paroxysmal pain and tactile allodynia in PHN patients.<sup>34</sup>

#### Other Topical Medications

**Capsaicin:** this topical agent has a small role in PHN management, but many patients tolerate its unpleasant, burning sensation poorly. One review concluded that a 0.075% preparation of capsaicin significantly improved pain in PHN patients<sup>6</sup>, although another found it had no effect.<sup>7</sup>

**NSAIDs:** there is inconclusive evidence about the efficacy of topical NSAID (non-steroidal anti-inflammatory drug) preparations for PHN.<sup>7</sup>

#### Nerve Blocks

Nerve blocks have been used to relieve pain from acute herpes zoster and PHN. However, this evidence stems from numerous anecdotal reports and case series, and nerve blocks have not been fully investigated in controlled clinical trials. Although sympathetic nerve blocks have been reported to relieve acute herpes zoster pain, there is no evidence that they are effective in treating PHN.<sup>7</sup>

#### Combination Therapy

Studies suggest that combination therapy may improve outcomes for patients with PHN. A randomized, double-blind, active placebo (lorazepam)-controlled, crossover trial in patients with neuropathic pain, including those with PHN, showed that those treated with combined gabapentin and sustained-release morphine had lower pain scores compared with monotherapy using either drug ( $p < 0.05$  for the combination vs placebo, gabapentin and morphine).<sup>35</sup> Furthermore, the required doses for each drug in the

combination therapy were lower than the doses required as monotherapy.<sup>35</sup> The reduction in opioid requirements was supported by a cross-sectional study (via a health insurance claims database review).<sup>36</sup> Among PHN patients receiving at least two prescriptions for gabapentin, the proportion of those receiving opioids decreased significantly upon the initiation of gabapentin (from 88.9% to 71.1%;  $p = 0.03$ ), as well as the mean number of opioid prescriptions per patient (from 3.9 to 3.0;  $p = 0.03$ ).

Patients who are poorly responsive to gabapentin-containing treatment may benefit from the addition of a 5% lidocaine patch. A 2-week, open-label, nonrandomized pilot trial on patients (including those with PHN) with poor analgesia from gabapentin-containing regimens found that daily application of up to four lidocaine patches to the areas of maximal peripheral pain may provide relief.<sup>37</sup> Patients reported significant improvements in Brief Pain Inventory measures of pain intensity, and pain interference with general activity, mood, walking ability, normal work, relationships with others, sleep and enjoyment of life. However, the investigators suggested controlled trials are necessary to define the impact of this regimen.

#### Nonpharmacological Management

##### Physical Methods

Allodynia is a common symptom of PHN. Application of a protective layer, such as cling film, between the skin and clothing can help to relieve allodynia. TENS can be useful for some patients, although limited success has been reported for ultrasound and acupuncture.<sup>7</sup> Physical therapy and occupational therapy

may also have a role in treating patients with chronic pain.

### Psychological Approaches

Patients with chronic pain often have complicated psychosocial problems and these should be carefully evaluated. Adequate information and explanation regarding the disease is helpful in alleviating any PHN-associated fears and anxieties. Cognitive behavioural therapy, relaxation training, biofeedback and self-hypnosis techniques are important methods in managing patients with intractable PHN. There is no strong evidence that psychological therapy is beneficial in PHN. However, psychological therapy has proved beneficial for other chronic pain syndromes and is likely to be beneficial for PHN.<sup>7</sup>

### Surgical Treatment

Numerous surgical procedures have been used to treat PHN including skin excision, sympathectomy, dorsal root entry zone lesions, cordotomy, thalamotomy, cingulumotomy, and spinal cord and deep brain stimulation. Invariably, studies have involved small patient numbers and have insufficient periods of follow-up.<sup>7</sup> Dorsal root entry zone coagulation and deep brain stimulation have not been shown to improve pain in PHN patients.<sup>38,39</sup> The results for spinal cord stimulation have been inconclusive and further studies are required.<sup>40</sup>

## V. Summary

Patients with PHN should be assessed by a full medical history and physical examination. It is important to provide patients with a detailed background of PHN and the proposed treatment plan. Every

patient's treatment must be planned individually. The proposed treatment algorithm for PHN is presented in the Figure. Initial treatment options include:

- tricyclic antidepressants, such as nortriptyline or amitriptyline;
- anticonvulsants, such as gabapentin or pregabalin;
- topical lidocaine or EMLA cream; and
- adjunctive TENS.

Patients who do not respond to these first-line therapies should be referred to a pain specialist for further investigation and management. Patients unresponsive to standard therapies may benefit from treatment alternatives, such as other anticonvulsants, tramadol, TENS, intrathecal methylprednisolone, NMDA antagonists, ATP or combination therapy, although there is less evidence for these treatments. A multidisciplinary approach involving a pain management physician, clinical psychologist and other allied health professionals may be required in treating these patients.

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