Managing neuropathic pain

Highlights from the 2014 Neuropathic Pain Certification Course

Neuropathic pain (NeP) remains one of the most challenging neurological problems encountered in clinical practice and represents a large area of unmet medical need. Although treatments targeting the underlying cause of NeP appear elusive, individualized multimodal interventions can provide meaningful pain relief to the patient.

On 8 and 15 June 2014, the Multidisciplinary Panel on Neuropathic Pain (MPNP) organized a Neuropathic Pain Certification Course in Hong Kong. The well-attended program convened a multidisciplinary panel of experts to discuss best practices and address some of the most pertinent issues in the contemporary management of NeP. This article summarizes the highlights of the meetings.

Overview of neuropathic pain

Initially referred to as pain due to peripheral neuropathies, the definition of NeP was expanded to include “pain initiated or caused by a primary lesion, dysfunction or transitory perturbation of the peripheral or central nervous system,” and more recently, “pain caused by a lesion or disease of the somatosensory system.”

Several major guidelines are currently available for the assessment and treatment neuropathic pain, namely guidelines of the International Association for the Study of Pain (IASP)’s Special Interest Group on Neuropathic Pain (NeuPSIG), the European Federation of Neurological Societies (EFNS), and the National Institute for Health and Care Excellence (NICE; UK).

A standard diagnostic workup may include use of screening tools, clinical examination and laboratory tests. Widely used screening tools include the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), the Neuropathic Pain Questionnaire (NPO), Douleur Neuropathique en 4 Questions (DN4), painDETECT and ID-Pain. Some of the NeP descriptors common to these tools include: pricking, tingling, and pins and needles; electric shocks and shooting; and hot and burning pain.

Albeit useful in differentiating NeP from nociceptive pain, screening tools do not provide conclusive evidence, or confirm a diagnosis, of NeP. A clinical examination should therefore be performed to verify or reject the hypothesis of a lesion or disease of the somatosensory system, as well as to map out areas of sensory abnormalities. Given the generally poor correlation between disease pathology and pain experience, laboratory tests can be used to assess function of the nervous system. Some of the most reliable tools include quantitative sensory testing, microneurography and skin biopsy, all of which are aimed at assessing the nociceptive pathways.

The approach to NeP management is often multimodal – usually requiring trials of physical, pharmacological and surgical interventions to achieve adequate pain relief. Prescribing pharmacotherapies for NeP is one of the key roles of the pain clinician. Although there is no consensus on optimal treatment, various recommendations have been developed for first-, second- and third-line pharmacotherapy based on the level of evidence for the different treatment strategies.

First-line treatments for NeP may be grouped into three classes: antidepressants (tricyclic antidepressants [TCAs], selective serotonin-norepinephrine reuptake inhibitors [SNRIs]); alpha-2-delta (δ2) ligands (gabapentin, pregabalin); and topical lidocaine (lidocaine patch 5%). Despite both being first-line treatment choices for NeP, pregabalin has been shown to have distinct pharmacokinetic advantages over gabapentin, including a predictable linear pharmacokinetic profile and a high oral bioavailability. In addition, fewer adverse events were observed in a cohort of NeP patients who
substituted gabapentin with pregabalin.\textsuperscript{15}

Tramadol and strong opioids are generally recommended as second-line treatment options except in certain specific clinical situations in which they can be considered for first-line use. Other agents such as carbamazepine and capsaicin are considered as third-line therapy. In addition, the guidelines recognize that combination therapy may improve analgesic efficacy and reduce side effects.\textsuperscript{3-5}

A four-step approach has been proposed to guide treatment of NeP (Table 1). More recently, Freeman and colleagues used cluster analytic techniques to identify distinct pain characteristic profiles that may reflect distinct pathophysiological mechanisms and, thus, potential differential responses to treatment.\textsuperscript{16}

Table 1. Stepwise approach to NeP treatment (adapted from Dworkin et al [2007])\textsuperscript{17}

<table>
<thead>
<tr>
<th>Step</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1</td>
<td>• Establish the diagnosis of NeP; if uncertain of the diagnosis, refer to a pain specialist&lt;br&gt;• Treat the cause of NeP</td>
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<tr>
<td>2</td>
<td>• Start therapy for the disease causing NeP&lt;br&gt;• Start symptom treatment with one or more of the first-line drugs&lt;br&gt;• Consider non-pharmacological treatments</td>
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<tr>
<td>3</td>
<td>• Reassess pain&lt;br&gt;• If pain is responsive to treatment, continue treatment&lt;br&gt;• If partial pain response, add one of the other first-line drug options&lt;br&gt;• If minimal pain response at target dose after an adequate trial, switch to an alternative first-line drug</td>
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<tr>
<td>4</td>
<td>• If trials of first-line drugs and in combination fail, consider second- and third-line drugs or referral to a pain specialist</td>
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Post-herpetic neuralgia

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Post-herpetic neuralgia (PHN) is one of the most common and debilitating complications of herpes zoster (HZ). Affecting an estimated 9–34% of all patients with HZ, PHN is generally defined as pain persisting more than 3 months after resolution of lesions.\textsuperscript{18,20} The psychological distress and physical disability associated with PHN have profound effects on a patient’s health-related quality of life and healthcare utilization.\textsuperscript{21,22} Therefore, improved understanding of the risk factors for HZ and PHN, as well as their effective interventions, are important to public health.

PHN is characterized by acute NeP, commonly described as deep aches, burning, stabbing, allodynia and hyperesthesia. The risk of PHN is high in HZ patients aged over 60 years – 30% and 75% in those >60 years and >70 years, respectively. Other risk indicators of PHN include severity of rash and acute pain.\textsuperscript{23}

PHN can be difficult to diagnose as it may occur long after the rash has cleared up. Thorough history-taking and physical examination are key to establishing the diagnosis, although laboratory investigations may be useful in cases with atypical presentation and possible herpes simplex infection.

Acyclovir, valacyclovir and famciclovir are the mainstay treatments for HZ and have been shown to decrease the severity and duration of acute HZ.\textsuperscript{24} Inconsistent evidence suggest that these antiviral agents may reduce the incidence of PHN or shorten the duration of symptoms.\textsuperscript{24-27} Prophylactic corticosteroids and amitriptyline have been shown to be preventive, but lack supporting evidence from clinical trials.\textsuperscript{28,29} Vaccination remains the best way to prevent PHN – a single dose of the HZ vaccine was found to reduce HZ burden of illness by 66.1% and PHN incidence by 66.5%.\textsuperscript{30} However, its use is contraindicated in immunocompromised individuals as well as those taking antiviral medications active against the HZ virus.\textsuperscript{31,32}

Besides guidelines from the USA, Canada and Europe, regional guidelines such those developed in the Middle East and in Hong Kong (The MPNP Recommendations for the Management of PHN) are available to guide pharmacotherapy for PHN.\textsuperscript{3,4,33} TCAs, α\textsubscript{2}δ ligands and topical lidocaine are typically recommended as first-line options, while SNRIs, opioids and tramadol are second-line options. A newer agent – topical capsaicin (8%) patch – is recommended as a first-line treatment option in the EFNS guideline.\textsuperscript{34,35}

Safety and tolerability of therapies are of critical importance in PHN/NeP management. A recent safety evaluation of pregabalin suggested that titration to the highest tolerable dose may be an appropriate approach in clinical practice. Common side effects, such as dizziness and somnolence, were shown to resolve without necessitating treatment discontinuation.\textsuperscript{36}

Referral to a pain specialist should be made for patients refractory to initial pharmacological interventions. Alternative treatment modalities, such as sympathetic blockade, intrathecal steroids and implantable spinal cord stimulators, have been shown to provide pain relief and may be considered.\textsuperscript{35} In addition, a multidisciplinary team which includes anaesthetists, neurologists, geriatricians and physiotherapists are integral to the continuum of care of patients with PHN.
Neuropathy is a common complication of diabetes, affecting 60–70% diabetic individuals. Of these, an estimated 25% suffer from painful diabetic neuropathy (PDN) – an NeP phenotype that can affect many aspects of a patient’s life and severely limit daily functions, such as walking and sleeping. In addition, pain is significantly correlated with depression in diabetic patients. A further complicating factor is that nearly half of diabetic patients do not discuss their NeP or its symptoms with their physician. In addition, chronic pain due to PDN does not always resolve despite control of glycemic levels.

The mechanisms by which hyperglycemia leads to structural nerve damage include accumulation of polyols by aldose reductase, formation of advanced glycation end products, and increased production of free radicals. PDN affects the peripheral nerves, typically small fibres (Aδ and C), large fibres (Aα/β) or both. However, small-fibre neuropathy usually precedes that of the large fibres, and is first manifested in the lower limbs. Symptoms associated with small-fibre dysfunction include hyperalgesia, numbness and autonomic dysfunction. Effects of large-fibre damage include deep-seated gnawing and aching pain, muscle wasting, and deficits in vibratory sense and proprioception. There is also evidence that even prediabetic patients with impaired glucose tolerance and normal HbA1c levels may have small-fibre neuropathy and experience pain.

Routine nerve conduction studies and electromyography are used to rule out subclinical involvement of large fibres. Two tests commonly used to confirm the diagnosis of small-fibre neuropathy are skin biopsy for the evaluation of intraepidermal nerve fiber density, and quantitative sudomotor axon reflex testing for the assessment of sudomotor autonomic function.

Diagnosis of PDN should be based on both clinical and objective measures. In addition to a detailed medical history and measurement of peripheral nerve function, a neurological examination assessing the sensory symptoms is essential. Sensory symptoms can be broadly divided into positive and negative. Positive symptoms include spontaneous pain, allodynia, hyperalgesia, dysesthesia and paresthesia. Negative symptoms comprise hypoesthesia, anesthesia, hypoalgesia and analgesia.

A detailed history of pain supplemented with the use of pain descriptors and pain rating scales can aid clinicians in the identification of patients with NeP and subsequent treatment decision-making.

The management of PDN should aim to improve glycemic control, exclude other causes of painful peripheral neuropathy, and alleviate pain using pharmacotherapy. International and regional PDN guidelines, including those of the EFNS, the IASP, the Canadian Pain Society, and the MPNP, recommend TCAs and α2δ ligands as first-treatment options. The EFNS and the IASP also recommend first-line use of the SNRIs venlafaxine and duloxetine. Tramadol and opioids are generally recommended as second-line treatments. Among these agents, pregabalin appears to have the largest evidence-base in the treatment of PDN and is the only A-level recommended drug in the updated American Academy of Neurology guideline.

Pregabalin is thought to exert effects within the cortex, and prior to the ascending pathways to reduce the release of pain-related neurotransmitters. Clinically, it has been shown to significantly reduce PDN pain, and reductions were positively correlated with dose. Significant improvements in sleep, anxiety and global mental health were also noted in pregabalin-treated patients with PDN.

Sciatica is term that describes a symptom of an underlying medical condition rather than a specific disease. It is generally characterized by pain or discomfort caused by injury to or pressure on the sciatic nerve, which begins from the lower spine and ends in the lower limb. The majority of cases of sciatica are neuropathic in origin (ie, described as burning, shooting or electric-like pain) and are related to a lesion in the sciatic nerve or its branches – a classic example is lumbar radiculopathy.
Chronic pain affects 11–55% of patients who experience a stroke. One of the most common forms of chronic post-stroke pain is central post-stroke pain (CPSP) which occurs in 8–35% of stroke patients. Often confused with other pain conditions associated with central nervous system (CNS) disorders, CPSP is currently defined as neuropathic pain that arises as a direct consequence of a lesion or disease affecting the central somatosensory system. There are no standard diagnostic criteria for CPSP – medical and pain history, clinical and sensory examination, and imaging of the lesion by CT or MRI are essential in establishing a diagnosis. As CPSP is a less common aetiology encountered in clinical practice, a diagnosis cannot be made without excluding other possible causes of central NeP. Examples may include, but are not limited to, multiple sclerosis, spinal cord injury, syringomyelia, vascular malformation and CNS infection. CPSP may be spontaneous or evoked, and is localized in the affected extremities. Pain qualities such as burning, aching, pricking, lancinating, shooting, squeezing and throbbing are common complaints, and they can occur in a continuous or in an intermittent fashion. Allodynia and dysesthesia are often detected by bedside testing, and these conditions rarely occur in pain-free stroke patients with similar somatosensory deficits. CPSP is widely distributed throughout the contralateral hemibody, but the pain can be limited to the face, trunk, or an extremity.
The pathophysiology of CPSP is not well established, but clinical characteristics of the disease, such as sensory loss (deafferentation), hypersensitivity (sensitization and disinhibition), and decreased or increased sensation of temperature and pain, are likely to be the underlying mechanisms.72

As with other NeP conditions, CPSP presents significant treatment challenges. While options and efficacy remain limited, treatments that lower neuronal hyperexcitability appear to be the most effective approach.72 Agents with such a mechanism include amitriptyline, lamotrigine, gabapentin and pregabalin.72,78 The MPNP guidelines recommend pregabalin and amitriptyline as first-line options, with lamotrigine, gabapentin, SNRIs and opioids considered as second-line options. Adjunctive local anaesthetic is placed as a third-line option.79

Besides CPSP, pain experienced after a stroke also include hemiplegic shoulder pain (HSP) (22–40%), spasticity-related pain (19–36%) and headaches (11–54%).80-87 These conditions can be extremely debilitating to a stroke patient.

HSP restricts the patient’s ability to undertake daily activities of daily living and evidence now suggests that HSP is likely to be neuropathic in origin.88 Major pain guidelines, such as those by the Scottish Intercollegiate Guidelines Network (SIGN) and the NHS Quality Improvement Scotland (NHS QIS), place emphasis on the prevention and treatment of HSP in the integrated care pathway for stroke.89,90 There is inconclusive evidence to support the use of botulinum toxin type A injections in HSP, whereas functional electrical stimulation was found to provide no benefit.91,92

Frequently occurring following upper motor neuron lesions, spasticity is characterized by a velocity-dependent increase in tonic stretch reflexes.93 Following stroke, approximately 30% of individuals develop spasticity, a condition which can be can be pervasive and debilitating.84 Currently approved pharmacotherapies for spasticity include baclofen, tizanidine, dantrolene and botulinum toxin.93 Other therapies that may be considered are mirror therapy, aromatherapy, acupressure, neuromuscular electrical stimulation and surgery.

Headache can occur a few days before and after stroke, and is particularly common in those who have a prior history of headaches. Vestergaard and colleagues reported that headache was lateralized in one third of patients, usually ipsilateral to the stroke lesion.94 This form of headache is often mild in intensity and may not require specific treatment, although simple analgesics, and sometimes narcotic analgesics, may provide relief.95

In recognition of the concurrent medical and psychological problems in patients with chronic pain after stroke, the MPNP recommends a holistic management approach that includes physical therapy, mood and sleep therapy, counseling and cognitive behavioural therapy.

**Trigeminal neuralgia**

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Often described as the “most terrible pain known to man,” trigeminal neuralgia (TN) is defined by the IASP as sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve.1

The prevalence of TN is estimated to be 0.1–0.2 cases per 1,000 persons, with annual incidence rates that range from 4–5 per 100,000 persons up to 20 per 100,000 persons after age 60.1,94 In addition, TN disproportionately affects women and the pain is almost always unilateral.96

TN can be classified as typical – generally characterized by paroxysmal pain alone – or atypical – which is associated with both paroxysmal and constant pain.97 The International Headache Society (IHS) defines TN based on aetiology as classical (idiopathic) or symptomatic (secondary).98 Classical TN includes all cases without established aetiology or those that may involve vascular compression of the trigeminal nerve. Symptomatic TN is considered when the pain syndrome is secondary to other diseases or abnormalities, including tumours, arteriovenous malformation or multiple sclerosis.97,99 Younger age of onset, abnormal trigeminal nerve reflexes, trigeminal sensory deficits, and bilateral pain, are strong indicators of symptomatic TN, but their absence does not necessarily indicate classical TN.100,101

A prompt and accurate diagnosis of TN is crucial because, if left untreated, the pain can become severe.99 The IHS has published diagnostic criteria to aid in differentiating classical from symptomatic TN (Table 2).98 However, in clinical practice, classical/idiopathic TN is a diagnosis of exclusion and relies upon patient history. Some of the more common differential diagnoses include...
temporal tendinitis, Ernest syndrome, occipital neuralgia, glossopharyngeal neuralgia, post-herpetic TN, short-lasting unilateral neurolgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome and paroxysmal hemicrania.102 Imaging modalities, such as MRI, can verify the diagnosis and rule out other causes of compression of the trigeminal nerve, such as tumours and vascular malformations.102

Past pain history should include pain descriptors such as shooting, stabbing, jabbing and electric shock sensation that occurs in paroxysms and around the trigeminal nerve.102 The key clinical feature of classical TN is sudden and severe lancinating pain lasting from a fraction of a second to 2 minutes. The pain is often triggered by minor sensory stimuli, such as talking, chewing or even a slight breeze to the face.97,99

Treatment of TN mainly involves pharmacological approaches. Current evidence-based guidelines recommend carbamazepine and oxcarbazepine as first-line options.102,103 Carbamazepine has strong evidence for efficacy, but oxcarbazepine has a better adverse effect profile.102 Pregabalin, gabapentin, lamotrigine, phenytoin, baclofen and amitriptyline are considered second-line options.102,103

There is insufficient evidence to recommend surgery for TN; however, it is generally considered for patients who are refractory to pharmacotherapy.103 Operative strategies can be broadly divided into four types: peripheral nerve blocks, percutaneous procedures, gamma knife surgery and microvascular decompression.103

Table 2. The International Headache Society criteria for the diagnosis of trigeminal neuralgia

<table>
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<tr>
<th>Classical (idiopathic)</th>
<th>Symptomatic (secondary)</th>
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<tr>
<td><strong>A. Paroxysmal attacks</strong> of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of the trigeminal nerve, and fulfilling criteria B and C</td>
<td><strong>A. Paroxysmal attacks</strong> of pain lasting from a fraction of a second to 2 minutes, with or without persistence of acheing between paroxysms, affecting one or more divisions of the trigeminal nerve, and fulfilling criteria B and C</td>
</tr>
<tr>
<td><strong>B. Pain has at least one of the following characteristics:</strong></td>
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<tr>
<td>1. Intense, sharp, superficial, or stabbing</td>
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<tr>
<td>2. Precipitated from trigger zones or by trigger factors</td>
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<tr>
<td><strong>C. Trigeminal attacks are stereotyped in the individual patient</strong></td>
<td><strong>C. A causative lesion, other than vascular compression, has been demonstrated by special investigations and/or posterior fossa exploration</strong></td>
</tr>
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References