In the feature article in this issue of Challenges in Neuropathic Pain, we present an overview on the relationship between neuropathic pain and mood disorders. Other articles in this issue cover the latest definition of neuropathic pain and pain-related terms from the International Association for the Study of Pain, and the case of a patient with neuropathic pain arising from a brachial plexus tumour. Visit www.neuropainhk.org for more resources on neuropathic pain from the Multidisciplinary Panel on Neuropathic Pain (MPNP).

### Review on the relationship between neuropathic pain and mood disorders

**Chronic pain** is common in Hong Kong. The prevalence of chronic pain lasting longer than 3 months has been reported to be 34%. Patients with chronic pain usually have increased incidence of physical disability, insomnia, anxiety, depression and overall poor quality of life. Their chronic pain condition may be difficult to treat, resulting in repeated visits to outpatient clinics or admissions to hospital.

Mood disorders are common in patients with chronic neuropathic pain, with the incidence being higher than that reported in the general population. According to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), the pain disorder diagnoses assume that some pains are associated solely with psychological factors, some with medical diseases or injuries, and some with both. There is a lack of evidence that such distinctions can be made with reliability and validity, and a large body of research has demonstrated that psychological factors influence all forms of pain. Most individuals with chronic pain attribute their pain to a combination of factors, including somatic, psychological, and environmental influences.

Abnormalities in the pain and mood modulating systems in the brain and spinal cord as well as dysfunction of the limbic system have been implicated as possible mechanisms for the occurrence of mood disorders in chronic pain. Pregabalin and antidepressants are effective for managing mood disorders in chronic neuropathic pain. As the perception of chronic pain is influenced by neural mechanisms, mood disorders, cognitive and affective traits as well as social, cultural, environmental and family factors, a multidisciplinary approach including physical rehabilitation and psychological and behavioural therapies is warranted for improving the physical and overall functioning of these patients.

### Epidemiology of mood disorders in chronic neuropathic pain

Mood disorders are widely prevalent in patients with chronic neuropathic pain. A retrospective cross-sectional study in 216 pain patients presenting to a neurodiagnostic clinic specializing in chronic, severe, and complex industrial injuries, involving complex combinations of nociceptive, neuropathic, and myofascial
pain in the United States (US) found that 44.4% of the patients suffered from major depressive disorder.

Similarly, a study in 182 patients with chronic peripheral neuropathic pain attending neurology practices and pain departments in France showed that lifetime and current prevalence rates for any mood disorder were 47.2% and 29.7%, respectively, and 39% and 20.3%, respectively, for any anxiety disorder. Major depressive episode (current prevalence, 16.5%) and generalized anxiety (current prevalence, 12.1%) were the two most common psychiatric disorders. Of note, these prevalence rates are higher than those reported in the general population. For instance, population studies in Europe and the US showed that the lifetime prevalence rates of mood disorder were 14% and 20.8%, respectively.3,6

Catastrophizing refers to a set of negative pain-related feelings such as helplessness and pessimism in relation to the ability to deal with pain, and a tendency to exaggerate the threat value of pain.4 High catastrophizing score (≥35/52 on the pain catastrophizing scale) was significantly associated with current mood disorders (odds ratio [OR], 6.9; 95% confidence interval [CI], 2.2 to 21.0) in the French study.4 Furthermore, moderate-to-severe minimal pain intensity in the last 24 hours predicted mood disorders (OR, 3.6; 95% CI, 1.4 to 8.9; p=0.02) whereas polyneuropathy was associated with a lower frequency of mood disorder (OR, 0.32; 95% CI, 0.13 to 0.79, p=0.01).4

Unlike paroxysmal pain, minimal pain is generally constant. This may impair the ability to cope with pain and lead to emotional distress and development of a mood disorder.4

**Table. Recommendations for managing neuropathic pain and psychiatric disorders**

<table>
<thead>
<tr>
<th>Guidelines for managing</th>
<th>1st line recommendations/Level A rating</th>
<th>2nd line recommendations/Level B rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>The European Federation of Neurological Societies (EFNS) 2009a</td>
<td>Pregabalin, gabapentin, TCAs, opioids, lidocaine plasters, capsicain 8% patch</td>
<td>Capsaicin cream, valproate</td>
</tr>
<tr>
<td>American Association of Neuromuscular and Electrodagnostic Medicine (AANEM), American Academy of Neurology (AAN), American Academy of Physical Medicine &amp; Rehabilitation (AAPPAR) 20111</td>
<td>Pregabalin</td>
<td>Gabapentin, duloxetine, venlafaxine, sodium valproate, amitriptyline, tramadol, oxycodone, capsicain</td>
</tr>
<tr>
<td>The International Association for the Study of Pain (IASP) 20102</td>
<td>Pregabalin, gabapentin, TCAs, SNRIs, topical lidocaine</td>
<td>Opioid analgesics, tramadol</td>
</tr>
<tr>
<td>The Canadian Pain Society (CPS) 20077</td>
<td>Pregabalin, gabapentin, TCAs, gabapentin, SNRIs, topical lidocaine</td>
<td>SNRIs, tramadol opioids</td>
</tr>
<tr>
<td>French-speaking Maghreb 2011</td>
<td>Pregabalin, gabapentin, TCAs, topical lidocaine</td>
<td>SNRIs, tramadol</td>
</tr>
<tr>
<td>Guidelines for managing psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>World Federation of Societies of Biological Psychiatry (WFSBP) 2012 – Generalized Anxiety Disordera</td>
<td>Pregabalin, escitalopram, paroxetine, sertraline, venlafaxine, duloxetine, quetiapine</td>
<td>Diazepam, lorazepam, hydroxyzine</td>
</tr>
<tr>
<td>American Psychiatric Association (APA) 2010 – Major Depressive Disorderb</td>
<td>Desvenlafaxine, duloxetine, venlafaxine, SSRIs, TCAs, nefazodone, trazodone, mirtazapine, MAOIs, NDRIs</td>
<td></td>
</tr>
</tbody>
</table>

MAOI, monoamine oxidase inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRl, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants

Correlation between severity of pain and a patient’s well-being and function

In patients with neuropathic pain, there is a direct relationship between pain severity and various aspects of well-being and function.11 Increased severity of pain is often associated with reduced function and increased mood disturbance.11 In the French study described above, 69% of the patients experienced sleep disturbances due to neuropathic pain. Severe pain intensity was independently associated with sleep disorders and impaired quality of life.4

A survey in 255 subjects with painful diabetic peripheral neuropathy in the US found that pain substantially interfered (≥4 on 0–10 scale) with walking ability, normal work, sleep, enjoyment of life, mood, and general activity. Greater severity of pain corresponded with higher symptom levels of anxiety and depression, more sleep problems, and lower utility ratings and physical and mental functioning (p<0.001 for all comparisons) than less severe pain.12

A study in 254 patients with posttraumatic neuropathic pain showed significant associations (p<0.001) between changes in pain and changes in patient-reported sleep disruption, pain interference on daily functions, and mood (ie, anxiety and depression).11

**Treatment of mood disorders, sleep and physical functioning in patients with neuropathic pain**

An important consideration while selecting a specific medication for treating neuropathic pain is its efficacy in decreasing pain as well as the associated symptoms, such as anxiety, depression and sleep disturbances, to ultimately improve the patient’s quality of life.13 The commonly recommended medications for managing chronic neuropathic pain and psychiatric disorders are summarized in Table.

**Efficacy of pregabalin**

Several studies have shown that pregabalin is effective in decreasing pain and improving the comorbidities associated with neuropathic pain.14-16 In a randomized placebo-controlled study among patients with posttraumatic neuropathic pain (n=254), pregabalin was also associated with significantly greater improvement in the mean endpoint pain score versus placebo (mean treatment improvement of the limbic system structures such as the amygdala and hippocampus is believed to contribute to disturbances in neuroendocrine, autonomic and immune functioning that may further contribute to the generation and/or worsening of mood and pain symptoms.4

Data from an animal study suggest that mood disorders in chronic neuropathic pain might be the result of functional impairment in noradrenergic circuits associated with areas of the brain (eg, locus coeruleus and prefrontal cortex) where emotional and sensorial pain processes overlap.9

One study found a correlation between wind-up ratio (WUR; increased responsiveness to repeated noxious stimuli in depressed patients) and serotonergic activity both in healthy controls (n=18) and depressed patients (n=18) combined (r=0.340, p=0.043). This indicates that WUR may be modulated by serotonergic activity and suggests that inhibitory control to noxious stimuli is partly associated with the central serotonergic function.18

Possible mechanisms for development of mood disorders in chronic pain

While the exact mechanism underlying the association between chronic pain and psychiatric problems is not known, abnormalities in pain and mood modulating systems in the brain and spinal cord have been suggested as a common mechanism.3 Mood disorders and chronic neuropathic pain are likely to coexist because these conditions share the same central nervous system pathways.9 Furthermore, dysfunction of the limbic system structures such as the amygdala and hippocampus is believed to contribute to disturbances in neuroendocrine, autonomic and immune functioning that may further contribute to the generation and/or worsening of mood and pain symptoms.4

For instance, population studies in Europe and the US showed that the lifetime prevalence rates of mood disorder were 14% and 20.8%, respectively.3,6
difference, -0.62; 95% CI, -1.09 to -0.15; p=0.01). Moreover, pregabalin showed improvements from baseline in pain-related sleep interference, and the Medical Outcomes Study sleep scale sleep problems index and sleep disturbance subscale (all p<0.001). Intention-to-treat analysis showed that pregabalin was associated with a statistically significant improvement in the Hospital Anxiety and Depression Scale anxiety subscale (p<0.05).

An observational study in 1,354 subjects with chronic peripheral neuropathic pain found that pregabalin, both as monotherapy and add-on therapy, for 12 weeks caused substantial improvement in severity of pain as well as in the associated disorders such as sleep disturbances, mood disorders, disability, and health-related quality of life.

A randomized controlled trial in 104 diabetic subjects with chronic diabetic peripheral neuropathic pain showed that amitriptyline, duloxetine, and pregabalin had comparable analgesic efficacy in reducing pain. However, pregabalin improved sleep continuity (p<0.001), whereas duloxetine increased awake and reduced total sleep time (p<0.01 and p<0.001).

Role of antidepressants
Antidepressants are effective in neuropathic pain and in improving mood disorders and sleep in those with chronic pain. The efficacy of antidepressants in chronic neuropathic pain may be related to the common pathways between depression and pain. However, it is believed that the analgesic effect of antidepressants is, at least partly, independent of their effect on depression. The dose required to achieve analgesia is, typically, lower than that required for antidepressant therapy.

Importance of multidisciplinary approach in chronic neuropathic pain
Besides neural mechanisms, perception of chronic pain is influenced by comorbid mood disorders, cognitive and affective traits such as catastrophizing and fear-avoidance, environmental stressors, family relationships, social support and cultural beliefs. Thus, it is important to undertake a multidisciplinary approach to treatment that includes pharmacotherapy as well as non-pharmacological treatments such as physical rehabilitation and psychological and behavioural therapies. This will serve to address the multifactorial causes of chronic pain and, consequently, improve physical and psychological functioning.

CASE PRESENTATION

Neuropathic pain due to brachial plexus tumour

Presentation
A 35-year-old lady complained of a mass over the base of the right side of her neck for 1 year. She had numbness and shooting pain in the right upper limb. The mass grew larger progressively, with corresponding worsening of the shooting pain as the mass size increased. Numbness and shooting pain are common characteristics of neuropathic pain.

Physical examination did not reveal any sensory or motor deficit of the upper limb. Tinel sign was positive for the right lateral aspect of arm and forearm.

The patient had nocturnal pain, and her activities of daily living and work were much disturbed by the pain. She was seen by a neurologist, an orthopaedic surgeon and a pain specialist. Various analgesic combinations were tried. The pain was partially under control with pregabalin 150 mg BID, acetaminophen 500 mg QID and tramadol 50 mg BID.

Investigation
Magnetic resonance imaging (MRI) revealed a nerve tumour – which was likely to be benign – arising from the right brachial plexus (Figure 1). As the patient had no neurological deficit, she was advised to try drug treatment before considering exploration and tumour excision.

The orthopaedic surgeon was concerned about iatrogenic nerve injury that might result in functional deficit of the upper limb.

Management plan
After much deliberation, the patient decided she did not want to rely on medication for the rest of her life. Therefore, the possible risks and benefits of surgery were discussed with the patient. The need for nerve grafting with possible donor site morbidity was also explained. She accepted the risks and opted for surgical exploration.

Exploration of right brachial plexus revealed a neurilemmoma arising from the upper trunk (Figures 2 and 3). The tumour was completely enucleated. The plexus was covered with Seprafilm to decrease chances of adhesion formation.

The neuropathic pain decreased significantly after the operation, and the patient had no neurological deficit. At 3 months, there was no neuropathic pain at all and the patient no longer requested pregabalin.

References
LITERATURE REVIEW

Definition of neuropathic pain

The International Association for the Study of Pain (IASP) in 2011 revised the definition of neuropathic pain to “pain caused by a lesion or disease of the somatosensory nervous system”. The previous definition, published by the IASP in 1994, was “pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous systems”. Other terms used to describe pain have also been updated since the original 1994 publication, including for allodynia and hyperalgesia. A summary of the IASP definition of neuropathic pain and other pain-related terms is presented in the Table.

The change in definition arose from a consensus process undertaken by a taskforce of expert physicians in collaboration with the IASP Special Interest Group on Neuropathic Pain. As described in a commentary by Jensen et al, the two key changes to the new definition are the removal of the word ‘dysfunction’ and specification of “lesion or disease of the somatosensory nervous system.” The authors explain the key reasons behind the new definition of neuropathic pain:

1. Neuropathic pain is a syndrome that is caused by a range of diseases and lesions rather than a single disease. Neuropathic pain is associated with a number of symptoms and signs such as allodynia and hyperalgesia (see Table for definitions), and various descriptions of pain such as burning, shooting and numbness. While mechanisms for some neuropathic pain conditions are known, many are still to be determined.

2. The new definition requires that the lesion within the nervous system must be within the somatosensory system. Hence, lesions within the areas of the brain, such as the cerebellum or frontal cortices, will not qualify as lesions causing central neuropathic pain unless future research reveals that they are part of the somatosensory system. The authors argue that distinct, precise clinical criteria will allow better-defined research on pathophysiology, epidemiology and specific treatments for a particular condition.

3. Current therapy for neuropathic pain is not sufficient, with more than two-thirds of neuropathic pain patients not obtaining satisfactory pain relief. This may be due to ineffective targeting of the mechanisms causing pain in individual patients. The authors suggest that furthering understanding of mechanisms of neuropathic pain is necessary, but that inclusion of pain conditions such as fibromyalgia and complex regional pain syndrome in the neuropathic pain condition will not be helpful as mechanisms underlying these conditions are less well known than for ‘classical’ neuropathic pain conditions. However, medications used to treat neuropathic pain conditions may still be of benefit in these patients.

Table. IASP definitions of neuropathic pain and pain-related terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Neurotic pain</td>
<td>Pain caused by a lesion or disease of the somatosensory nervous system</td>
</tr>
<tr>
<td>Central neuropathic pain</td>
<td>Pain caused by a lesion or disease of the central somatosensory nervous system</td>
</tr>
<tr>
<td>Peripheral neuropathic pain</td>
<td>Pain caused by a lesion or disease of the peripheral somatosensory nervous system</td>
</tr>
<tr>
<td>Allodynia</td>
<td>Pain due to a stimulus that does not normally provoke pain</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>An unpleasant abnormal sensation, whether spontaneous or evoked</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>Increased pain from a stimulus that normally provokes pain</td>
</tr>
<tr>
<td>Hypoalgesia</td>
<td>Diminished pain in response to a normally painful stimulus</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Pain caused by a lesion or disease of the somatosensory nervous system</td>
</tr>
<tr>
<td>Nociceptive pain</td>
<td>Pain that arises from actually or threatened damage to non-neural tissue and is due to the activation of nociceptors</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>An abnormal sensation, whether spontaneous or evoked</td>
</tr>
<tr>
<td>Sensitization</td>
<td>Increased responsiveness of nociceptive neurons to their normal input, and or recruitment of a response to normally subthreshold inputs (applies to both central and peripheral nervous systems)</td>
</tr>
</tbody>
</table>

References

Thank you to the general practitioners who completed the survey from the Hong Kong Pain Society (HKPS) and MPNP on the management of pain in general practice.

We sincerely appreciate the feedback that the survey has provided on the estimated case-load of chronic pain in general practice, and, in particular, information on the most commonly diagnosed neuropathic pain conditions and how neuropathic pain is managed in practice.

The results from the survey have provided insight and direction for future medical education initiatives.

MPNP ACTIVITIES

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