



Challenges in

Neuropathic Pain

Welcome to the 21st issue of *Challenges in Neuropathic Pain*, a newsletter from the Multidisciplinary Panel on Neuropathic Pain (MPNP). The feature article this issue provides a summary of the MPNP's recommendations on the management of neuropathic cancer pain. The series on non-pharmacological treatments for neuropathic pain continues, with a review of the evidence for acupuncture, while the case presentation is on chronic neck pain. Visit www.neuropainhk.org for more resources from the MPNP on neuropathic pain, including all previous issues of *Challenges in Neuropathic Pain*.

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Recommendations on the management of neuropathic cancer pain

The Multidisciplinary Panel on Neuropathic Pain first published recommendations on neuropathic cancer pain in 2006¹; this article provides a summary of the 2011 revision to the recommendations.

Epidemiology, pathophysiology and symptoms

An international survey on cancer pain by the International Association for the Study of Pain revealed that around 90% of patients experienced pain, of which 40% was caused by neuropathic mechanisms.² Cancer-associated pain may be secondary to antineoplastic therapy or an unrelated comorbid condition, but is commonly due to direct tumour involvement.³

Somatic pain originates from disorders of bone, joints, muscles or connective tissue.⁴ Bone pain syndromes are the most prevalent,^{3,4} while somatic pain from other sites can be due to the presence of inflammatory mediators, muscle spasms or postsurgical incisions or occur in patients undergoing radio- or chemotherapy. Visceral pain is caused by obstruction, infiltration or compression of visceral structures and supporting connective tissues.⁴ Visceral pain is often diffuse and sometimes referred to other non-visceral structures, making the source of pain difficult to localize.

Neuropathic pain is characterized by aching, burning, stabbing or lancinating pain, and may also present as paraesthesia, dysaesthesia, hyperalgesia or allodynia. It occurs in approximately 30% to 55% of cancer patients, although recent estimates in patients with head and neck cancer varied from 34% to 73%.^{5,6} Neuropathic pain is often due to tumour infiltration or compression of neural structures, while sympathetic activity also plays a role in spontaneous neuropathic pain.⁴ Most post-treatment pain syndromes (eg, following surgery, radiotherapy or chemotherapy) are neuropathic.⁴ Relative to somatic and visceral pain, neuropathic pain responds poorly to systemic opioids; hence, other treatments are often utilized.^{3,7}

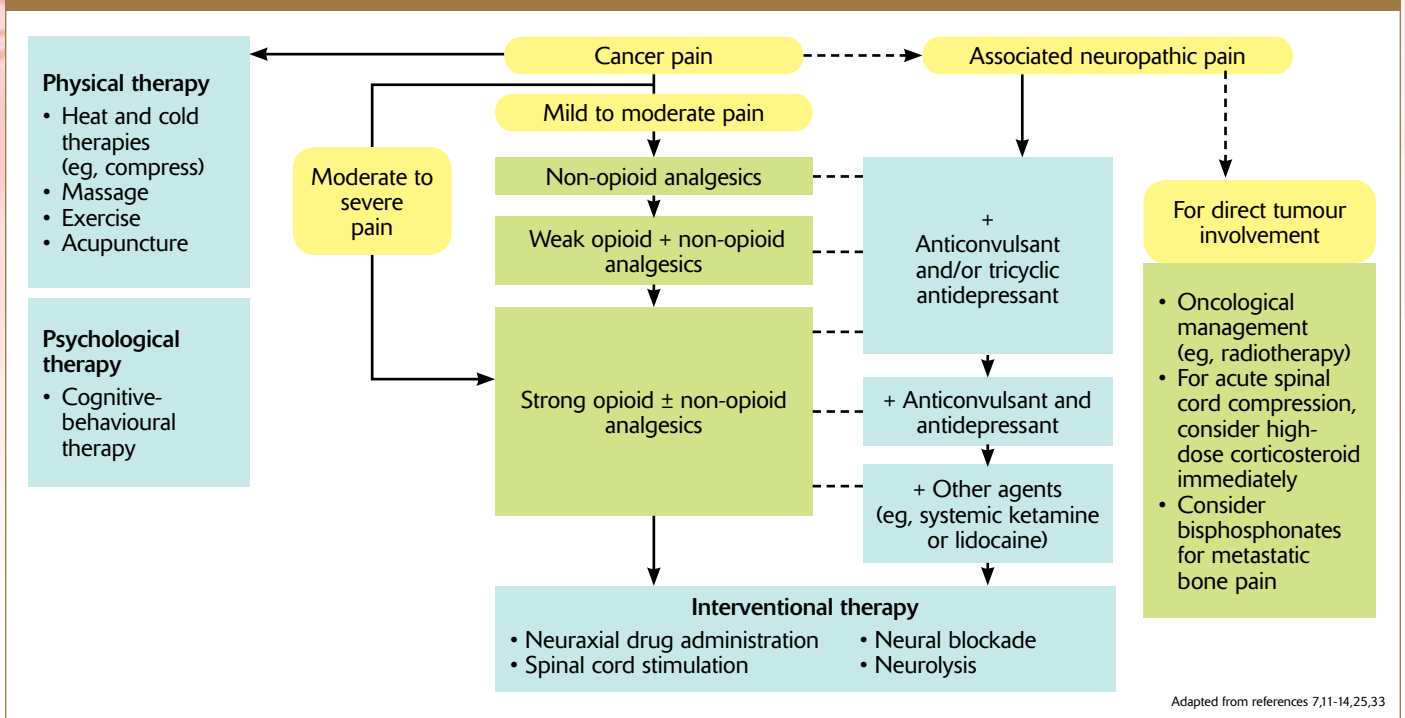
Assessment of cancer pain

- A detailed history and medical, physical and neurological examination should be performed to characterize and quantify pain, and to assess the primary cancer site and its relationship to the pain.⁴
- All components of pain (eg, intensity, characteristics, location, radiation, timing and effect on daily living) should be assessed to assist in identifying specific pain syndromes and monitoring progression and response.

Contact the Panel

Forward any comments on this newsletter to the Multidisciplinary Panel on Neuropathic Pain at mppnp@ubm.com.

Figure. Management of cancer pain



- Clinical assessment of neuropathic cancer pain may be challenging; currently no single method is available to reliably diagnose cancer-related neuropathic pain.⁸ However, a number of screening tools are available to help identify neuropathic pain. The ID Pain™ has recently been validated in breast cancer survivors,⁹ while the Neuropathic Pain Questionnaire (NPQ), Leeds Assessment of Neuropathic Signs and Symptoms (LANSS) and Neuropathic Pain Symptom Inventory (NPSI) may also help to identify neuropathic pain in cancer patients.¹⁰
- If a patient has neuropathic pain, nerve compression should be excluded as this requires immediate treatment. Analgesics should be instituted as early as possible even though full diagnosis is not yet established.¹¹
- Because of the progressive nature of most cancers and the changes that occur in cancer pain characteristics, assessment should be repeated at regular intervals. New reports of pain should also be noted.
- Patients who do not respond to adequate drug therapy may benefit from interventional techniques (Figure).
- Physiotherapy may reduce the need for analgesics.¹⁵ While physiotherapy should not be used as a substitute for medication, it should be introduced early to treat generalized weakness, deconditioning, and pain associated with inactivity and immobility. Psychological therapies, such as cognitive behavioural therapy, should also be instituted early to teach patients how to cope with pain.
- The management of cancer pain should be multimodal and multidisciplinary. Patients with terminal cancer often have significant emotional and mood disturbances, or other psychosocial issues, which need to be addressed. Some of these issues may be more important to the patient than the pain itself. Hospice care should be considered for such patients.

Management of cancer pain

General principles of cancer pain treatment

- Cancer treatments, such as surgery, chemo- or radiotherapy, may relieve pain by removing or reducing the size of the tumour thereby reducing compression or infiltration.¹²
- Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a role in managing somatic cancer pain, particularly for patients with bone metastasis.¹¹
- Pain caused by soft-tissue infiltration, visceral distention and increased intracranial pressure may be treated initially with corticosteroids.¹³ Acute spinal cord compression should be treated with intravenous dexamethasone or methylprednisolone. Surgical decompression of the brain or spinal cord and fixation of painful spinal fractures should be considered where appropriate.
- The World Health Organization (WHO) analgesic ladder for cancer pain relief advocates introducing analgesics in a stepwise manner according to response (Figure).^{7,11} However, pain that is moderate to severe at the outset should be treated with higher potency opioids or with higher doses.¹²
- Adjunctive therapies may be used with or without conventional analgesics at any stage (Table).¹⁴

For neuropathic cancer pain

- About 50% of all difficult to control cancer pain is neuropathic in origin.¹⁶ For neuropathic pain caused by direct tumour involvement, first-line management may include surgery, radiotherapy or chemotherapy.
- Correctable causes of neuropathic pain (eg, spinal cord compression) should be managed appropriately.
- Anticonvulsants (eg, pregabalin, gabapentin) and antidepressants (eg, amitriptyline, venlafaxine) are recommended adjuvant analgesics for cancer-related neuropathic pain (Figure).^{16,17} A recent systematic review revealed that use of antiepileptic and antidepressant agents as adjuvants to opioids improved pain control, although there is potential for an increase in side effects.¹⁸ Evidence is strongest for gabapentin.^{18,19} However, data from the United States reveal that use of these types of drugs is relatively low in neuropathic cancer pain.²⁰
- Ketamine may be effective, but because of its adverse effects should be limited to experienced teams.³ Other adjunctive therapies include systemic or topical lidocaine and topical capsaicin.^{6,21,22}
- A recent prospective study conducted in 818 patients with neuropathic cancer pain revealed that multimodal treatment following the WHO analgesic ladder is effective in the majority of patients; the main adjuvant drugs were gabapentin, amitriptyline and dexamethasone.²³

Table. Indications for adjunctive therapy in cancer pain management^{3,7,11-14}

Indication	Adjunctive therapy
Neuropathic pain	Anticonvulsants (eg, pregabalin, gabapentin) Antidepressants (eg, amitriptyline, venlafaxine) Other agents (eg, ketamine, lidocaine)
Metastatic bone pain	Bisphosphonates (eg, pamidronate)
Anxiety symptoms Emesis	Hydroxyzine
Poor analgesic response Increased intracranial pressure Spinal cord compression Perineural edema and nerve compression Nausea Anorexia and poor appetite Cachexia	Corticosteroids

• While there is little data on the role of complementary therapy in the management of neuropathic cancer pain, a recent review article described such treatments as massage, acupuncture, and psychological and behavioural approaches, which may be of use in managing neuropathic cancer pain.²⁴

• Interventional therapy may also be effective for neuropathic cancer pain.²⁵⁻³¹ However, certain interventional techniques for neuropathic pain should only be considered when pharmacological interventions have failed, are poorly tolerated or inappropriate.

• Ongoing assessment and communication with patients is important. In a study investigating patient perceptions associated with chemotherapy-induced peripheral neuropathy, patients reported that neuropathic pain interfered with daily life and expressed frustration, depression and loss of purpose.³²

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NON-PHARMACOLOGICAL TREATMENTS FOR NEUROPATHIC PAIN

In this issue, we present the second article in a series on non-pharmacological interventions for neuropathic pain with a discussion on acupuncture.

Part 2 – Acupuncture

Acupuncture, an integral component of Traditional Chinese Medicine, involves the use of needles inserted at specific acupoints. It is becoming increasingly common in Western countries as an alternative and complementary therapeutic intervention.¹⁻³ Clinical studies suggest that acupuncture may be useful in treating disorders of the nervous system, such as stroke and facial palsy, and provide analgesic effects in different pain conditions, including those of neuropathic origins.¹⁻³

In patients with diabetic peripheral neuropathy (DPN), acupuncture has been demonstrated to provide symptomatic ‘cure’ or improvement through the reduction of numbness and providing significant pain relief and/or reducing spontaneous pain.^{4,5} This reduction in DPN symptoms has also been objectively confirmed by nerve conduction studies, which demonstrated improvements in measurements after 10 weeks of treatment.⁶

A recent systematic review on the efficacy of acupuncture in trigeminal neuralgia suggested that patients may achieve benefits from this treatment.² While some studies reported that acupuncture has similar efficacy to carbamazepine with fewer adverse events, most studies showed no significant differences between the acupuncture

and control groups.

Symptoms of cancer-related neuropathic pain have also been shown to improve following acupuncture, with treatment effects correlated with physiological measurements and imaging techniques.⁷ In addition, a recent meta-analysis of controlled clinical trials reported that acupuncture provided small analgesic effects for fibromyalgia patients.⁸

Although acupuncture has produced promising results in patients with specific neuropathic pain conditions, no conclusive evidence is available to substantiate its benefits. Also, these trials had small sample sizes and were conducted with heterogeneous methodologies (eg, treatment protocols, controls and endpoints, inadequate blinding). Further large-scale randomized controlled trials are required to validate these existing studies and to confirm the benefits of acupuncture treatment in neuropathic pain patients.^{2,4-6}

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Q & A

Forward any questions on neuropathic pain to the MPNP at mpnp@ubm.com.

What resources are available for neuropathic pain patients in Hong Kong?

Chronic pain can be a debilitating and frustrating condition for many patients. Neuropathic pain, in particular, may be difficult to manage with patients potentially suffering for many years. Patients with neuropathic pain symptoms in whom the diagnosis is unclear or with neuropathic pain that is refractory to treatment may be referred to pain clinics or specialists, such as neurologists, for assessment and management. Multidisciplinary pain clinics are established in most major Hospital Authority (HA) hospitals and some private hospitals, while neurology clinics are in most hospitals. A prospective study examining

the profile and referral pattern of patients attending an outpatient pain management service in Hong Kong revealed that 28% had neuropathic pain.¹

The MPNP has developed educational materials for patients – including a leaflet and a poster – that are available for download at www.neuropainhk.org/PatientEducationMaterials.aspx. The Hong Kong Pain Society (www.hkpainsociety.org) also provides a resource on pain management in Hong Kong, with the Web site including some information for patients on chronic pain.

Reference

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CASE PRESENTATION

The topic for the case presentation in this issue is chronic neck pain.

Chronic neck pain

Presentation

The patient is a 38-year-old female who injured her neck and back during a fall in her office 4 and a half years ago. She developed chronic back pain and left-sided sciatica, neck pain and arm numbness. The pain has persisted for more than 2 years, despite physiotherapy and medications.

Clinical investigation and interventions

The left sciatica extended from the buttock to above the knee. Physical examination revealed tenderness and muscle spasm over the lower back. Extension of the back increased back pain and left sciatica. Left straight leg-raising test was positive at 45 degrees. An MRI scan of the lumbar spine showed mild lumbar prolapsed intervertebral disc (PID) and annulus tear on the left side at L5/S1 level. Left L5/S1 transforaminal lumbar epidural steroid injection was performed. Back pain and sciatic pain were reduced by 80%.

The neck pain increased on turning the head. Pain radiated down the left arm, and there was also numbness in the left arm. Physical examination showed tenderness at left C5/6 facet joints and referred pain down the left arm. An MRI scan of the cervical spine showed mild cervical C5/6 PID without nerve compression. Diagnostic left C5 and C6 dorsal median branch nerve block (ie, left C5/6 facet joint nerve

Figure. Positioning of radiofrequency needles at the lateral surface of C5 and C6 facet joint columns



block) significantly reduced pain. Left cervical C5/6 facet joint radiofrequency neurolysis was performed (see Figure). The pain and left arm numbness largely resolved. Two years after treatment, the back pain, sciatica, neck pain and left arm numbness remain well controlled.

Discussion

Neuropathic pain in the arm and leg after accidental spinal injury is not always caused by nerve compression. Inflammation around the torn annulus of an intervertebral disc and the nerve sheath of the spinal nerve root may produce sciatica. Chronic cervical facet joint pain can radiate to the shoulder, arm and scapular region. With appropriate diagnostic tests, including diagnostic nerve block, the source of the pain can be identified. Good pain relief can be achieved with minimal invasive procedures.

Source: MPNP members

LITERATURE REVIEW

Moon DE, Lee DI, Lee SC, et al. Efficacy and tolerability of pregabalin using a flexible, optimized dose schedule in Korean patients with peripheral neuropathic pain: A 10-week, randomized, double-blind, placebo-controlled, multicenter study. *Clin Ther* 2010;32:2370-2385.

The efficacy and tolerability of pregabalin in Korean neuropathic pain patients was assessed in a 10-week, randomized, double-blind, placebo-controlled multicenter phase III study. Mean Daily Pain Rating Scale (DPRS) score was the primary study outcome. Secondary outcome measures included the Daily Sleep Interference Scale (DSIS), Medical Outcomes Study (MOS) Sleep Scale and Hospital Anxiety and Depression Scale (HADS).

A total of 240 patients with peripheral neuropathic pain due to diabetic peripheral neuropathy, postherpetic neuralgia or post-traumatic neuropathic pain were randomized 2:1 to receive either pregabalin (150–600 mg/d; n=162) or placebo (n=78). Patients on a stable dose of selected analgesics were permitted to continue their medications for the study period. Patients recorded daily responses in a pain diary – consisting of DPRS and DSIS – upon waking and were followed-up weekly throughout the study. Patients also completed the MOS sleep scale and HADS, at the start (week 0) and end (or discontinuation) of the study.

After 8 weeks of treatment, the pregabalin group achieved significantly lower mean DPRS score (least squares mean difference, -0.50; 95% CI: -1.00–0.00; p=0.049) than the placebo group. Significantly more pregabalin-treated patients reported an at least 50% reduction in mean DPRS score from baseline compared with placebo-treated patients (26.1% vs 14.3%; p=0.041). Weekly mean DPRS scores were also significantly lower for pregabalin-treated patients at weeks 4 and 8 (p<0.05). Statistically significant improvements in secondary measures

such as sleep quality and anxiety were also reported by patients in the pregabalin group.

The authors concluded that flexible-dose pregabalin was associated with significant pain reduction, and improvements in anxiety symptoms and sleep quality in neuropathic pain patients. It provided additional pain relief even with concomitant use of other analgesics. In this study, no serious adverse event was recorded with pregabalin use and its safety and tolerability profiles were consistent with that of previous studies in other populations.



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